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Pathology

418. **Serial Study of Bone Marrow in Hemolytic Disease of the Newborn (Erythroblastosis Fetalis)**
H. C. DILLON and W. KRIVIT. *Pediatrics* [*Pediatrics*] **23**, 314–322, Feb., 1959. 4 figs., 26 refs.

It has been suggested that failure of erythrocyte production plays an important part in the genesis of the anaemia of haemolytic disease of the newborn, and the term " aregenerative anaemia " has been used to describe it. In this paper from the University of Minnesota the results of serial observations of the percentage of normoblasts in the bone marrow of 12 infants with erythroblastosis during the first 60 days of life are considered in relation to the degree of anaemia and the reticulocyte levels in the peripheral blood.

In only one of the 12 cases did the percentage of normoblasts fall below the reported values for normal infants of the same age, and that was in a child who had received 3 exchange transfusions. In all other cases the proportion of normoblasts in the marrow was increased above the normal level at all ages and was inversely related to the degree of anaemia, whether it was mild or severe. The possible fallacy of assessing marrow activity from the peripheral reticulocyte level is pointed out. Both from the results of the present study and from a critical review of the literature it is concluded that cessation of erythropoiesis in the anaemia of erythroblastosis is a rare occurrence.

[It is obvious that in this as in other haemolytic anaemias the frequency of the rare aregenerative or hypoplastic crisis has been exaggerated, and unwarranted generalizations made from observations on a few exceptional cases.] *A. G. Baikie*

MORBID ANATOMY AND CYTOLOGY

419. **Rubella in Pregnancy. Fetal Pathology in the Internal Ear**
J. E. GRAY. *Annals of Otology, Rhinology and Laryngology* [*Ann. Otol.* (*St Louis*)] **68**, 170–174, March, 1959. 4 figs., 6 refs.

This report from the University of Durham describes the findings in the internal ears of a 53-mm. human foetus whose mother developed a severe attack of rubella on the 37th day of pregnancy, the foetus being removed 12 weeks after the last menstrual period because of the mother's mental state.

The basal coil of the cochlea on both sides showed marked abnormalities, the chief finding being a cytoplasmic lysis of the basilar membrane. Examination of the rest of the cochlea provided no explanation for this, and it seemed unlikely that the condition was produced by changes in the blood vessels.

William McKenzie

420. **Further Observations on the Pathology of Pulmonary Emphysema in Chronic Bronchitics**
B. E. HEARD. *Thorax* [*Thorax*] **14**, 58–70, March, 1959. 13 figs., 9 refs.

In a previous paper (*Thorax*, 1958, **13**, 136; *Abstr. Wld Med.*, 1958, **24**, 401) the author described a method for demonstrating the pathology of pulmonary emphysema by impregnating slices of lung with barium sulphate. In this further study from the Postgraduate Medical School of London slices were prepared in this way from the lungs of 3 normal persons, a girl aged 6½ and 2 men aged 50 and 69 years respectively, and examined under the dissecting microscope. In the lungs of the girl the diameter of the respiratory bronchioles was about 0·2 mm. and of the alveoli 0·1 mm.; in the man aged 50 these figures were 0·2 to 0·4 mm. and 0·1 to 0·15 mm. respectively, while in the oldest subject they were 0·3 to 0·5 mm. and 0·15 to 0·2 mm. respectively. Dust pigment in the normal adult lung accumulates in the upper parts of the upper and lower lobes and collects near the centres of the secondary lobules, tending to avoid the fibrous septa. In the lungs of the man aged 69 there were some small bronchopneumonic patches, the distribution of which was similar within the lobule to that of centrilobular pigment and centrilobular emphysema.

Emphysema has previously been classified into centrilobular and diffuse types, but these types may be found combined and in a multiplicity of patterns. The author presents photomicrographs, with accompanying descriptions, of lung slices showing respectively mild diffuse emphysema, moderate diffuse emphysema, and mixed diffuse and centrilobular emphysema. In the case of mild diffuse emphysema illustrated the respiratory bronchioles could be seen at a distance of twice an arm's length by the naked eye (Gough's method) and reached 0·65 mm. or more in diameter. Most alveoli were about 0·2 mm. in diameter, but occasionally measured 0·25 or 0·3 mm. in diameter. In moderate diffuse emphysema the normal distinct pattern of respiratory bronchioles and alveoli is replaced by a less regular pattern of very thin air-space walls through which blood vessels are clearly visible. In the case illustrated there was a narrow zone of superficial emphysema where the

normal structure was replaced by a coarse network of pulmonary arteries with fibrosed remnants of respiratory tissue surrounding them.

Three cases are illustrated showing well marked, pigmented, centrilobular emphysema combined with diffuse emphysema of different grades in the peripheral parts of the lobule. The fact that diffuse emphysema is so often accompanied by centrilobular emphysema, and the frequent occurrence of both these conditions in chronic bronchitics, seem to suggest that diffuse emphysema, like the centrilobular variety, may be the end-result of acute inflammation. When the diffuse emphysema is extensive it is often difficult to decide whether infection was the cause or the effect. *G. Clayton*

421. **Honeycomb Lungs and Malignant Pulmonary Adenomatosis in Scleroderma**
H. CAPLAN. *Thorax* [*Thorax*] **14**, 89–96, March, 1959. 10 figs., 32 refs.

Two cases of scleroderma associated with cystic changes in the lungs and pulmonary adenomatosis are described [from Whittington Hospital, London]. In Case 1 the adenomatosis was possibly malignant, in Case 2 it was unequivocally so with metastases to pleura and diaphragm.

The appearances of cystic fibrosis of the lungs found in association with scleroderma are discussed. It is considered that these changes show no essential difference from those found in honeycomb lung and that the pulmonary fibrosis of scleroderma is similar to other pulmonary fibrosis or granulomata in being the antecedent of honeycomb lung.

The relation of "tumourlets" and pulmonary adenomatosis to carcinoma and the pathogenesis of hyperplastic respiratory epithelium are discussed. The hypothesis is put forward that the hyperplastic epithelial changes are in some way related to impaired respiratory function associated with increased pulmonary fibrosis.—[Author's summary.]

422. **Cardiac and Renal Manifestations in Progressive Systemic Scleroderma**
E. N. ROTTENBERG, C. H. SLOCUMB, and J. E. EDWARDS. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **34**, 77–82, Feb. 4, 1959. 3 figs., 5 refs.

Nine patients with generalized scleroderma were studied at necropsy with special reference to cardiac and renal lesions. Seven had myocardial fibrosis, which was attributable to scleroderma in 4. Only 2 of the patients without other causes of heart failure and with myocardial fibrosis exhibited congestive heart failure. In one of these the heart failure was a prominent clinical feature, while in the other it appeared to contribute to the death caused primarily by carcinomatosis.

Renal lesions of significance were observed in 3 of the patients, each dying of uremia. The renal lesions of scleroderma form a characteristic picture, with multiple arterial occlusions and cortical infarcts. Hypercellularity of glomeruli with fibrinoid necrosis of the basement membranes of the glomerular tuft is occasionally observed. The vascular lesions are impossible to distinguish from those of primary hypertension, but taken with the presence of multiple cortical infarcts and glomerular changes like those seen in lupus erythematosus they form a complex that appears to be specific for the kidney of scleroderma.—[Authors' summary.]

423. **The Structural Basis of Proteinuria in Man. Electron Microscopic Studies of Renal Biopsy Specimens from Patients with Lipid Nephrosis, Amyloidosis, and Subacute and Chronic Glomerulonephritis**
D. SPIRO. *American Journal of Pathology* [*Amer. J. Path.*] **35**, 47–73, Jan.–Feb., 1959. 18 figs., 22 refs.

The structural basis of proteinuria was studied in the Pathology Department, Massachusetts General Hospital (Harvard Medical School), Boston, in percutaneous renal biopsy specimens obtained from 3 patients with the nephrotic syndrome (one with juvenile "pure" lipid nephrosis and 2 with amyloidosis) and 2 with proteinuria (one with subacute and one with chronic glomerulonephritis). Part of each specimen was used for conventional histological examination and the remainder was examined in an electron microscope. In all the specimens defects were seen with the electron microscope in the basement membrane of the glomerular loops which may constitute the structural basis of proteinuria. *A. Wynn Williams*

424. **The Small Tumour-like Lesions of the Kidney**
A. J. M. REESE and D. P. WINSTANLEY. *British Journal of Cancer* [*Brit. J. Cancer*] **12**, 507–516, Dec., 1958. 14 figs., 25 refs.

A study was undertaken in the Department of Pathology of the Royal College of Surgeons of England to determine the frequency and nature of the small tumour-like nodules found from time to time in either the cortex or the medulla of the kidney. A single kidney was taken from each of 212 unselected necropsy subjects, mostly adults, and fixed for at least 2 weeks in 10% formol saline. Slices about 0·12 cm. thick were then cut in an electric ham slicer. Blocks for histological examination were taken from all those slices which contained solid nodules, 5-μ sections being cut and stained with haemalum and eosin.

With a few exceptions every tumour-like lesion found fell into one of 4 categories: (1) ectopic adrenal tissue; (2) cortical adenomata; (3) fibrous medullary nodules; or (4) hamartomata, which included "leiomyomata", "lipomata" and "mixed lipomyomata". Adrenal rests were present in 10 (4·7%) of the kidneys examined and were always placed superficially. Cortical adenomata were found in 31 (14·6%) of the kidneys; they were considered to be true neoplasms and became commoner as age advanced. Fibrous nodules of the medulla occurred in 78 (36·8%) of the kidneys and were also more common in the elderly; they were regarded as "focal overgrowths" of fibrous tissue. Leiomyomata, lipomata, and mixed lipomyomata were found in 6%, 7%, and 6% of kidneys respectively, were present at all ages, but were commoner in females than in males.
A. Wynn Williams

Microbiology and Parasitology

425. **Epidemic Staphylococci**
R. E. O. Williams. *Lancet* [*Lancet*] **1**, 190–195, Jan. 24, 1959. Bibliography.

Over the 4-year period 1954–7 some 3,803 strains of staphylococci isolated from septic lesions in hospital patients during "epidemics" of infection were received for identification at the Staphylococcus Reference Laboratory, Colindale, London. The results have been analysed and compared with the information in published accounts of epidemics in an attempt to learn something about the spread of staphylococcal infection in hospitals. A study of 32 outbreaks in maternity units showed that the organism responsible probably came from a healthy carrier in 8 of the outbreaks and from a nurse with some form of superficial infection in 5. Baby-to-baby spread was clearly concerned in 5 outbreaks, while in a further 7 infection from infant to nurse and from nurse to infant probably occurred as well. There were reports of 15 outbreaks of surgical sepsis; in one a patient probably infected in the operating theatre from a septic lesion on the surgeon's hand was the source, while in 4 outbreaks healthy carriers among the nurses and among the surgeons were the primary sources of the organisms. In the remaining outbreaks no source could be discovered.

Phage-typing of the 3,803 strains of staphylococci showed that over 50% of the recognized epidemic spread was due to 6 phage types. One of the most interesting findings was that whereas Type 80 comprised only 14·9% of the strains from infections submitted for typing in 1954, it formed no less than 30·1% of those typed in 1957. *R. Hare*

426. **The Relationship between Poliomyelitis Antibody and Virus Excretion from the Pharynx and Anus of Orally Infected Monkeys**
D. E. Craig and G. C. Brown. *American Journal of Hygiene* [*Amer. J. Hyg.*] **69**, 1–12, Jan., 1959. 11 refs.

The relationship between the presence of antibody to poliomyelitis virus and excretion of the virus was studied in a number of experimental animals at the University of Michigan, Ann Arbor. A virulent neurotropic strain of Type-1 poliomyelitis virus was fed in a dosage of 100 oral infectious virus units to 14 monkeys which had been vaccinated with a commercial poliomyelitis vaccine but had not developed antibodies and to 14 control monkeys. The virus was recovered from the throats of all but one of the animals up to 13 days after feeding and from the anus intermittently during the first 4 days and again from the 6th to 9th days. Paralysis developed in 13 of the controls and in 9 of the vaccinated animals. Excretion of the virus continued until death in those animals dying before the 10th day and before antibody developed, but in animals which survived until the 10th to 12th days antibody was detected on the day of paralysis and the virus had disappeared. Virus was isolated from the throats of 8 and from the anus of 15 out of 16 vaccinated monkeys with homologous antibody, but, with two exceptions, only during the first 3 days. Paralysis developed in 6. The antibody titre did not appear to be directly correlated with the development of paralysis. Of 10 monkeys with homologous antibody as a result of previous administration of live virus, in one of which paralysis developed, virus was isolated from the anus of all only during the first 3 days and from the throat of one on a single occasion only. The presence of heterologous antibodies induced by feeding live virus in 15 monkeys did not modify the pattern of recovery of the virus from either the throat or the anus from that observed in the control animals. *A. Ackroyd*

427. **Purified Protein Derivatives (PPD) and Other Antigens Prepared from Atypical Acid-fast Bacilli and *Nocardia asteroides***
L. F. Affronti. *American Review of Tuberculosis and Pulmonary Diseases* [*Amer. Rev. Tuberc.*] **79**, 284–295, March, 1959. 6 figs., 25 refs.

Recent reports of an association between atypical acid-fast bacilli and human pulmonary infection have stimulated the author to investigate, at the University of Pennsylvania, the chemistry and antigenic relationship of five of these organisms which had been isolated from patients with such disease, 2 obtained from Kansas City and 2 from the Battey State Hospital, Rome, Georgia, being strains of the photochromogenic "yellow bacillus" and the fifth being a strain of *Nocardia asteroides*. These organisms were grown on a synthetic liquid medium and purified protein derivates (P.P.D.) prepared from each of them. Antisera were also made to each strain in rabbits.

Each strain was found to have characteristic cultural and microscopical appearances, which are described. Chemical analysis of the P.P.D. preparations showed that over 90% of each extract consisted of protein, while the carbohydrate content varied from 5·9% in one of the Kansas City strains to 0·8% in *N. asteroides*; there was also considerable variation (between 2·1% and 0·05%) in the proportion of deoxyribonucleic acid present. The latter figure, for the strain of *Nocardia*, did not correspond with the figure found for the spectral density in the ultraviolet-light curve, and this organism was found to have the bulk of its nucleic acid present as ribonucleic acid. The results of precipitin tests, agar-gel diffusion analyses (by the Oakley–Fulthorpe technique), and skin tests in rabbits and guinea-pigs showed that there was sharing of a number of antigens, but that it was possible to differentiate the organisms from each other by the precipitin technique. There was also evidence of antigenic relationship to the human strain of *Mycobacterium tuberculosis*. Skin sensitivity tests in rabbits and guinea-pigs confirmed these findings and showed that the organisms have a certain degree of antigenic specificity. *John M. Talbot*

Pharmacology and Therapeutics

428. **A Six-month Evaluation of an Anabolic Drug, Norethandrolone, in Underweight Persons. I. Weight Gain**

R. N. WATSON, M. H. BRADLEY, R. CALLAHAN, B. J. PETERS, and R. C. KORY. *American Journal of Medicine* [*Amer. J. Med.*] **26**, 238–242, Feb., 1959. 12 refs.

From Marquette University School of Medicine, Milwaukee, Wisconsin, the authors report the results of administration of the anabolic agent norethandrolone (" nilevar ") to three groups of volunteer subjects, comprising 28 healthy workers, male and female, 16 male long-term hospital patients (mean age 63 years), and 10 male tuberculous patients; in the last-named group the chest condition appeared to be stable in each case, the sputum being negative for tubercle bacilli and the erythrocyte sedimentation rate normal. These 54 subjects, all but 2 of whom were underweight, received daily for 3 months either a tablet of norethandrolone (25 or 50 mg.) or a placebo tablet, the double-blind technique being employed. The weight was recorded at regular intervals, the blood picture examined, liver function tests performed, together with radiography of the chest, urine analysis, and psychological assessment.

There was a consistent gain in weight in the subjects receiving norethandrolone, averaging 5½ lb. (3·4 kg.) in 12 weeks in the group receiving 25 mg. of the drug and 4·7 lb. (2·14 kg.) in those receiving 50 mg.; there was no significant weight change in the subjects receiving the placebo. At the end of 24 weeks the weight gains were 11 and 7·1 lb. (5 and 3·2 kg.) in the patients receiving 25 and 50 mg. respectively. Subjects transferred from the placebo to norethandrolone showed a significant weight gain in the second 12 weeks of the trial. The weight changes were accompanied by a sense of well-being, and many subjects developed a voracious appetite. Of the 10 female subjects studied, 8 developed side-effects which included menorrhagia, amenorrhea, and acne, these being more frequent in those given the higher dose and being reversed or reduced by decreasing the dosage of norethandrolone or discontinuing it; androgenic effects were not observed. There were no abnormal biochemical effects apart from increased " bromsulphalein " retention in the majority of the patients. The weight gained by the patients taking norethandrolone was maintained or increased in 19 out of 25 subjects followed up for 6 months after the drug was discontinued. The authors conclude that norethandrolone produces an impressive weight gain in underweight subjects, partly owing to its anabolic action and partly from the resulting increase in appetite. (It is noted that many of the patients studied had unsuccessfully attempted to gain weight before this trial by increasing their dietary intake.) The gain in weight observed was not associated with fluid retention, but was considered to be due to increased protein tissue mass. *A. E. Read*

429. **A Six-month Evaluation of an Anabolic Drug, Norethandrolone, in Underweight Persons. II. Bromsulphalein (BSP) Retention and Liver Function**

R. C. KORY, M. H. BRADLEY, R. N. WATSON, R. CALLAHAN, and B. J. PETERS. *American Journal of Medicine* [*Amer. J. Med.*] **26**, 243–248, Feb., 1959. 23 refs.

The second part of this paper describes an investigation which was carried out following the discovery of abnormal " bromsulphalein " retention in 47 out of the 54 subjects described above. Standard bromsulphalein retention tests (5 mg. of dye per kg. body weight) were performed 2, 4, and 6 months after the institution of norethandrolone therapy and continued after its withdrawal at weekly intervals until a normal result was obtained. Four other customary liver function tests were also performed. In addition 10 further subjects —male geriatric patients—were chosen for a short-term study, being given norethandrolone in doses of 25 and 50 mg. daily for 6 and 3 weeks respectively. Estimations of bromsulphalein retention and of the serum glutamic oxalacetic transaminase (S.G.O.T.) level were repeated at intervals during and after administration of the drug until these were normal in this group of subjects.

Bromsulphalein retention greater than 6% (the upper limit of normal) was found in 35 (74%) of 47 subjects of the long-term study, the retention exceeding 20% in 11 cases. Of these subjects, 2 developed " chemical jaundice " (serum bilirubin level 2·2 and 1·7 mg. per 100 ml. respectively) and a raised serum alkaline-phosphatase level; liver biopsy revealed biliary retention and focal hepatic necrosis in one of these cases. In 7 subjects with bromsulphalein retention ranging from 14 to 46% liver biopsy showed some increased cellular infiltration in the portal zones. In all the 10 subjects of the short-term study abnormal bromsulphalein retention developed in one to 4 weeks; the higher the dose of norethandrolone, the earlier did retention appear. The abnormal values returned to normal in 2 to 4 weeks. A small rise in S.G.O.T. level consistently accompanied the development of abnormal bromsulphalein retention, the two returning to normal together.

Among the possible mechanisms discussed it is suggested that an upset of the mechanism of transport of bromsulphalein, affecting either its uptake by the liver cells or its excretion into the biliary tract, is the most likely. It is concluded that whatever the reason, norethandrolone is potentially hepatotoxic and may produce cholestasis, particularly when given in high dosage. It is therefore recommended that when the drug is administered continuously for over one month serial measurements of the serum bilirubin and alkaline-phosphatase levels be performed in order to detect any important degree of cholestasis. Fortunately this picture is rare with low dosage, and it is regularly reversible on cessation of treatment. *A. E. Read*

430. **Results of a Clinical Trial of G–28315, a Sulfoxide Analog of Phenylbutazone, as a Uricosuric Agent in Gouty Subjects**

T. F. Yü, J. J. Burns, and A. B. Gutman. *Arthritis and Rheumatism* [*Arthrit. and Rheum.*] **1**, 532–543, Dec., 1958. 2 figs., 14 refs.

The modern treatment of gout depends on increasing the loss of urates from the body by giving drugs which depress renal tubular reabsorption of filtered urate. The phenylbutazone derivative sulphinpyrazone ("anturan"; G–28315) is such a drug. In this paper from Mount Sinai Hospital, New York, and the National Heart Institute, Bethesda, Maryland, the authors report their experiences with the clinical use of sulphinpyrazone in 44 patients with gout, of whom 42 were in the tophaceous stage, 12 had extensive deposits of urate, and 8 had persistent pain and stiffness between attacks.

In 29 patients the initial mean urate excretion per 24 hours was 509 mg., 25 of them showing a daily excretion of less than 600 mg. After treatment with sulphinpyrazone in a dosage of 400 mg. per day the mean daily excretion rose to 839 mg., being over 600 mg. in 25 cases. In 40 patients with an initial serum urate level over 7 (mean 10·7) mg. per 100 ml. this level fell to a mean of 7 mg. per 100 ml., 22 patients showing values below this. With the dosage of 400 mg. daily, however, only 7 out of 40 patients achieved normal serum urate levels (below 6 mg. per 100 ml.), but in some "resistant" patients the serum urate level fell further following an increase of the dosage to 600 or 800 mg. per day. Reduction in the size of visible tophi occurred in all but 4 of 20 patients followed up for over 7 months. Side-effects, mostly mild, occurred on 18 occasions in 12 patients; they included dyspepsia and gastro-intestinal upset (5 cases), renal colic and/or calculus (8), and a flare-up of acute gouty arthritis (5). Insufficient time has elapsed to assess any long-term hazards. A combination of sulphinpyrazone and zoxazolamine had a synergistic action in one patient. Four illustrative case histories are presented to show that some patients were tolerant of sulphinpyrazone but intolerant of other uricosuric drugs and *vice versa*. The authors conclude that sulphinpyrazone is a useful addition to the several uricosuric drugs at present available. *Allan St. J. Dixon*

431. **Decrease in Oxygen Consumption Associated with Prolonged Administration of the Carbonic Anhydrase Inhibitor, Acetazolamide (Diamox)**

S. M. Tenney and N. Tschetter. *American Journal of Medical Sciences* [*Amer. J. med. Sci.*] **237**, 23–26, Jan., 1959. 9 refs.

It has been shown that the carbonic anhydrase inhibitor acetazolamide ("diamox") is a valuable therapeutic agent in the management of certain cases of respiratory insufficiency associated with emphysema. It has also been suggested that, apart from its diuretic action, acetazolamide may lower the metabolic rate, possibly on account of some antithyroid activity derived from its sulphonamide structure. The present study was undertaken at Dartmouth Medical School, Hanover, New Hampshire, to investigate this possibility. Rats weighing approximately 200 g. were divided into 3 test groups. Group 1 received 4 mg. of acetazolamide per kg. body weight daily intraperitoneally for 40 days, Group 2 received 8 mg. per kg., also for 40 days, and Group 3 received 50 mg. per kg. for 30 days; the two control groups were given daily injections of acidified distilled water. Body weight was recorded throughout the experiment and oxygen consumption was determined on resting unanaesthetized animals over a one-hour period. At the end of the experiment the animals were killed, the organs weighed, and pooled samples of blood obtained from each group for determination of the serum protein-bound iodine content.

The rats receiving acetazolamide were easily identified during the latter half of the test period by their less active state and by the fact that they ate less and gained weight less rapidly. The metabolic rate was significantly reduced by acetazolamide in each test group, but for no obvious reason this reduction was less marked in Group 3 (receiving 50 mg. per kg.). The serum protein-bound iodine level was also most markedly depressed in Group 3. The weight of the thyroid gland was increased in all groups, but the increment was never of more than borderline statistical significance. The authors suggest that these experiments demonstrate an effect of the long-term administration of acetazolamide on oxygen consumption and carbon dioxide production, and may therefore provide some explanation for the lowering of CO_2 tension obtained in certain cases of respiratory insufficiency without producing any associated increase in ventilation. The increase in weight of the thyroid gland and the decreases in the serum protein-bound iodine level in the treated animals suggests that acetazolamide may be an antithyroid agent, although this conclusion must still be regarded as tentative. *John Lister*

432. **The Differing Mechanisms of Action of Mercurials, Carbonic Anhydrase Inhibitors, and Chlorothiazide as Diuretic Agents**

R. V. Ford and J. B. Rochelle. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **53**, 53–63, Jan., 1959. 7 figs., 1 ref.

This paper from Baylor University College of Medicine and the Veterans Administration Hospital, Houston, Texas, describes the use of the combined administration of two or three different diuretics to patients with congestive cardiac failure as a means of analysing the mechanism of such drugs. The doses given were those producing maximum sodium excretion. Acetazolamide led to a further rise in urinary sodium excretion if given after the maximum response had been obtained with meralluride and vice versa. Similarly, chlorothiazide further increased sodium excretion after the maximum response had been obtained with either meralluride or acetazolamide, but in this case the reverse did not apply with either drug. From these findings it is inferred that acetazolamide and meralluride act at different sites, whereas chlorothiazide shares one point of attack with meralluride and another with acetazolamide, but in addition increases sodium excretion by another mechanism. When chlorothiazide was administered as

the third drug after both meralluride and acetazolamide had been given a further rise in sodium excretion was still obtained. This indicates that chlorothiazide does not act like a combination of the other two drugs, but produces its effect by yet another mechanism.

R. Schneider

433. **Localization of the Site of Action of Chlorothiazide by Stop-flow Analysis**

A. J. VANDER, R. L. MALVIN, W. S. WILDE, and L. P. SULLIVAN. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol. exp. Ther.*] **125**, 19–22, Jan., 1959. 2 figs., 10 refs.

The technique of "stop-flow" analysis [see August, 1959, Abstr. 239] was used to study the effects of the non-mercurial diuretic, chlorothiazide, on renal tubular function in dogs anaesthetized with pentobarbitone. The drug was shown to reduce the ability of the proximal tubule to reabsorb water, sodium, and potassium. As with the mercurial diuretics, the concentrations of these ions in the fluid reabsorbed remained similar to those in the plasma. Distal tubular secretion of potassium was increased, and there appeared to be some inhibiting effect on its distal reabsorption. Like the mercurials, chlorothiazide was without effect on the capacity of the distal tubule to reduce sodium concentration.

W. C. Bowman

434. **Comparative Experimental Studies of Some New Sulphonamides with Diuretic and Saluretic Activity.** (Vergleichende experimentelle Untersuchungen über neue Sulfonamide mit diuretischer und saluretischer Wirkung)

J. J. CHART, A. A. RENZI, W. BARRETT, and H. SHEPPARD. *Schweizerische medizinische Wochenschrift* [*Schweiz. med. Wschr.*] **89**, 325–331, March 21, 1959. 5 figs., bibliography.

In experiments on dogs and rats carried out at the Ciba Laboratories, Summit, New Jersey, on a number of new heterocyclic sulphonamide compounds hydrochlorothiazide was shown to be up to 21 times more potent as a diuretic and saluretic than chlorothiazide. It was found to inhibit the sodium-retaining effect of deoxycortone acetate and aldosterone and, like chlorothiazide, to have a hypotensive action. Hydrochlorothiazide is very effective when given by mouth and has a remarkably low toxicity.

G. S. Crockett

435. **Fall of Blood Pressure after a Noradrenaline Infusion and Its Treatment by Pressor Agents**

J. H. BURN and M. J. RAND. *British Medical Journal* [*Brit. med. J.*] **1**, 394–397, Feb. 14, 1959. 6 figs., 10 refs.

In this paper from the University of Oxford the authors describe experiments carried out on spinal cats which show that the pressor action of certain sympathomimetic amines is potentiated by an intravenous infusion of noradrenaline (65 μg. per minute for about 30 minutes). The amines whose action is potentiated include "methedrine" (methylamphetamine), "mephine" (N-methylphenyl tertiary butylamine), and vonedrine (phenylpropylmethylamine), all of which appear to act by liberating noradrenaline from its store. Three other compounds—"aramine", "vasoxine", and "propadrine" (all derivatives of phenylethanolamine)—have some direct action as well as some action in discharging the store of noradrenaline, and thus do not have so great a pressor action at the end of a noradrenaline infusion as they otherwise would. Lastly, noradrenaline, adrenaline, and dopamine have a diminished pressor action after an infusion of noradrenaline. Hence the authors recommend that when the blood pressure falls to a low level after an intravenous drip infusion of noradrenaline has been stopped the right procedure is not to resume the infusion, but to inject methedrine, mephine, or vonedrine or, if these are not available, aramine, vasoxine, or propadine.

G. B. West

436. **The Action of Nitrites on the Cardiovascular System.** (Azione dei nitriti sull'apparato cardiovascolare)

A. MEDA, G. EINAUDI, and V. NAZZI. *Minerva medica* [*Minerva med. (Torino)*] **49**, 4327–4334, Nov. 24, 1958. 34 refs.

The cardiovascular effects of glyceryl trinitrate were studied at the University of Turin in 20 subjects aged 20 to 60 (average 52·2) years, 8 of whom were healthy, while 6 were suffering from hypertension and 6 from coronary insufficiency (patients with proved severe coronary damage or myocardial infarction being excluded). The drug was given in doses of 0·4 to 0·6 mg., observations being made before and immediately, 10 minutes, and 20 minutes after its administration, while in some cases the period of observation was longer. The data recorded for each subject at these intervals comprised systolic and diastolic arterial pressure, pulse rate, stroke volume, cardiac output (minute volume), peripheral resistance (calculated from the mean arterial pressure and the cardiac output), and the calculated cardiac work. All these data are expressed as percentage increase or decrease over the basal values, absolute values being given only for arterial pressure and pulse rate.

The drug caused a fall in systolic pressure, reaching its maximum after 10 minutes and usually lasting more than 20 minutes, in nearly every subject, the fall being greatest in the hypertensive group. The effect on the diastolic pressure was much less. The pulse rate increased in almost all subjects, rising by an average of 9·5, 6·8, and 7·5% in the normal, coronary, and hypertensive groups respectively immediately after the dose. The stroke volume fell by 12·5, 33·3, and 18·1% respectively in the three groups immediately after the dose, the minute volume decreasing by slightly less in each group, and at the same time the peripheral resistance increased in all groups, the rise being least in the normal group. In all three groups the calculated cardiac work was decreased throughout the period of observation, the fall being greatest in the hypertensive and coronary groups (maximum 34·7 and 32·5% respectively) and least in the control group (17·5%).

In view of these findings it is concluded that the administration of nitrites is likely to cause a reduction in coronary blood flow. Although the effect of this will be offset by the reduction in cardiac work and therefore in myocardial oxygen requirements, the authors suggest

that these drugs should be used with caution in cases of acute coronary failure.

[The conclusions reached are not those generally accepted and it is a great pity that the authors have given such scanty details of their experimental methods that it is impossible for the reader to judge for himself the validity of the data presented.]

W. H. Horner Andrews

437. **The Action of the Halothane–Diethyl Ether Azeotropic Mixture on Experimental Animals**

J. RAVENTÓS and J. DEE. *British Journal of Anaesthesia* [*Brit. J. Anaesth.*] **31**, 46–52, Feb., 1959. 2 figs., 5 refs.

An azeotropic mixture of volatile liquids is one in which the two liquids distil in constant ratio at constant boiling temperature. Such a mixture is formed by halothane and diethyl ether (in the proportion of about 2:1), and it has been claimed that it has advantages in clinical use over halothane. This paper from a pharmaceutical research laboratory reports a careful comparison of the effects of halothane and the azeotropic mixture on mice, cats, and dogs.

The 50% anaesthetic concentration (AC_{50}) and lethal concentration (LC_{50}) of the azeotrope were significantly higher than those of halothane, but there was only a slight difference in respect of the LC_{50}:AC_{50} ratio (which is an index of the safety margin of a compound) in mice. The two substances showed no difference in their effects on the blood pressure, heart rate, and respiration in cats; nor was there any difference in the degree to which halothane and the mixture produced extrasystoles in cats given adrenaline, except in one cat in which extrasystoles appeared with the azeotrope but not with halothane.

The presence of ether in the mixture does not make it explosive in the concentration needed for maintenance of anaesthesia, but it might be explosive if the azeotrope were used in concentrations above 3·5% during induction, particularly in the presence of nitrous oxide and oxygen.

Ronald Woolmer

438. **Evaluation of a New Analgesic Agent: D-Propoxyphene Hydrochloride (Darvon)**

G. VALENTINE and S. J. MARTIN. *Anesthesia and Analgesia; Current Researches* [*Anesth. Analg. curr. Res.*] **38**, 50–55, Jan.–Feb., 1959. 12 refs.

After a brief account of the chemistry and pharmacology of propoxyphene (" darvon "), a synthetic analgesic agent first introduced in 1953, the authors describe their own investigation of the drug at St. Francis Hospital, Hartford, Connecticut, in the first part of which it was given to 100 patients orally in a 65-mg. capsule together with 0·4 mg. of atropine subcutaneously 60 to 90 minutes before they underwent " elective operation ". The results were compared with those in 100 patients who were similarly premedicated with 75 to 100 mg. of pethidine and 0·4 mg. of atropine given as above and 100 patients who received only the atropine and a placebo. Anaesthesia consisted of thiopentone followed by nitrous oxide and oxygen (60%:40%), ether, or cyclopropane. It was found that only the patients who had received pethidine exhibited sedation, euphoria, amnesia, or depression of the cardiovascular and respiratory systems; those given propoxyphene or the placebo were normally alert and showed no cerebral depression. With both analgesic agents less thiopentone was required for maintenance of anaesthesia than in the group given the placebo only.

In the second part of the study 196 patients who had undergone major surgery were studied by the double-blind technique, identical-appearing capsules containing 65 mg. of propoxyphene, 32·5 mg. of codeine phosphate, 0·325 g. of acetylsalicylic acid, or an inert substance being administered in doses of one capsule every 2 to 6 hours as required. It was found that the order of efficacy of these medications in relieving pain was as follows: propoxyphene, codeine, acetylsalicylic acid, placebo. The relief of pain with propoxyphene came on within one hour, reached a maximum in 100 minutes, and lasted from 120 to 310 minutes (average duration 240 minutes). No evidence of respiratory, cardiovascular, or cerebral depression was noted. Propoxyphene appears to be a promising mild analgesic agent for use by anaesthetists, but has the disadvantage that at present it is only available for administration by mouth.

Mark Swerdlow

439. **Enhancement of Sodium Salicylate Absorption and Clinical Effectiveness by Mephenesin**

R. C. BATTERMAN, J. CARR, and G. J. MOURATOFF. *Journal of the American Geriatrics Society* [*J. Amer. Geriat. Soc.*] **7**, 114–119, Feb., 1959. 3 figs., 12 refs.

In studies previously reported from New York Medical College (*Fed. Proc.*, 1958, **17**, 367) the authors showed that mephenesin increases the absorption of sodium salicylate in man. In the present study a combination of 500 mg. each of mephenesin and sodium salicylate was given orally to 46 subjects and produced, in comparison with the same dose of sodium salicylate given alone, a more rapid, more prolonged, and greater increase in the plasma salicylate level, the mean concentrations at 30 minutes being 4·67 and 1·46 mg. per 100 ml. respectively.

The clinical effect of the same dosage of mephenesin and sodium salicylate was studied in comparison with (1) a placebo; (2) sodium salicylate alone in doses of 300 to 600 mg.; and (3) aspirin in a dosage of 600 mg. 3 to 4 times daily for at least 3 weeks. With the combined drugs effective antirheumatic and analgesic responses were obtained in 69·5% of 59 patients suffering from various rheumatic disorders compared with 50 to 54% with sodium salicylate alone or aspirin. Further, the incidence of side-effects in patients given the salicylate alone was 40%, as against 11·9% in those receiving the combination with mephenesin. Although the higher plasma levels of salicylate achieved when mephenesin and sodium salicylate are given together does not explain this increased therapeutic efficacy, the more rapid rate of absorption of the combination may provide the answer and also account for the reduced incidence of gastro-intestinal symptoms.

Kenneth Gurling

Chemotherapy

440. **Experiments on the Antituberculous Activity of *alpha*-Ethyl-thio*iso*nicotinamide**
N. Rist, F. Grumbach, and D. Libermann. *American Review of Tuberculosis and Pulmonary Diseases* [*Amer. Rev. Tuberc.*] **79**, 1–5, Jan., 1959. 18 refs.

At the Pasteur Institute, Paris, experiments carried out *in vitro* and in animals with α-ethyl-thio*iso*nicotinamide, a derivative of *iso*nicotinic acid but not of isoniazid, revealed high activity against strains of tubercle bacilli resistant to isoniazid. The activity of this thioamide *in vitro* on tubercle bacilli grown in Youman's medium was one-tenth that of isoniazid and approximately the same as that of streptomycin, and, as with isoniazid, the bacilli ceased to be acid-fast. In experimentally infected guinea-pigs the thioamide was one-tenth as active as isoniazid, but twice as active as streptomycin. The toxicity of the drug for mice was one-fifth that of isoniazid but twice that of streptomycin. Resistant strains could be produced either by successive transfer *in vitro* or by experiments in mice, but when multiple drug regimens were used no resistant strains emerged.
I. Ansell

441. **The Salts Derived from the Combination of Streptomycin and Neomycin with Glucuronic Acid. The First Experimental Research on the Antibacterial Power and Ototoxic Effects of These Salts**
G. Rossi and A. Olivieri. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **69**, 188–196, Feb., 1959. 48 refs.

It has been known since 1946 that streptomycin has a specific neurotoxic effect on the vestibular nerve and also, though to a much less extent, on the cochlear nerve. Such damage is not relieved by any treatment, but usually there is some functional compensation for the vestibular nerve damage. The first attempt to avoid these effects was by the use of dihydrostreptomycin. This salt was found to cause little damage to the vestibular apparatus, but unfortunately often had a disastrous effect on the cochlear nerve. Trials reported by various authors of different salts of streptomycin showed the sulphate to be less toxic than the other common salts, but that while streptomycin pantothenate and phosphorylate showed diminished toxicity, they also had diminished antibacterial power. Glucuronic acid has itself some antibacterial action and for this reason the present authors, working at the Otolaryngological Clinic, University of Turin, selected streptomycin glucuronate for trial. Experiments *in vitro* and *in vivo* in rabbits and rats showed that the glucuronate was equally as efficacious as the sulphate in experimental infections, while the neurotoxic action of the glucuronate on the cochleo-vestibular apparatus in these experimental trials " appeared very slight and negligible ".

Neomycin is also a very powerful antibacterial agent, but parenteral use has been contraindicated by its toxic action on the kidneys and the auditory function. As with streptomycin, attempts have been made to reduce the dangers by the synthesis of new salts, in particular the pantothenate and phosphorated neomycin. However, as with streptomycin, the diminution of toxicity has been accompanied by diminution of antibacterial action. In trials similar to those described above the present authors found the glucuronate of neomycin to be as effective therapeutically as the sulphate, that it was less generally toxic, and that its neurotoxic action on the cochleo-vestibular apparatus, although not fully abolished, was noticeably less than that of neomycin sulphate.
F. W. Watkyn-Thomas

442. **Neomycin Ototoxicity. Report of a Case**
G. J. Greenwood. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **69**, 390–397, April, 1959. 7 figs., 29 refs.

Neomycin is claimed to have the widest antibacterial spectrum of all the antibiotics. It is least effective against the *Pseudomonas* group, but even here it is more effective than any other drug. It is widely used for local, superficial infections, where it is effective in small amounts, and for preoperative sterilization of the bowel, little being absorbed by the intact intestine. Unfortunately it is so toxic that its parenteral use is contraindicated except in extreme cases, when it should be given intramuscularly. The toxic action of the drug is greatest on the collecting tubules of the kidney and the hair cells of the cochlea, the vestibular hair cells not being affected so severely. The related drugs streptomycin and dihydrostreptomycin also show varying toxic affinity for the cochlea and vestibule. That the ototoxicity of this group of antibiotics is not limited to the labyrinth is suggested by the fact that dihydrostreptomycin has been shown also to affect the neuroglia of the acoustic pathway and auditory cortex.

The present author summarizes 20 cases of neomycin ototoxicity reported in the literature and adds one of his own. The damage in nearly all was much greater to cochlear than to vestibular function, and the risk of such damage seemed to be greatest when neomycin was given for the treatment of some urinary lesion. Various attempts have been made to reduce the toxicity of the drug, but it is difficult to do this without also reducing its efficacy. The calcium salt of pantothenic acid (one of the components of the vitamin-B complex) has been shown to reduce the acute toxicity of the streptomycin group, and a close association of vitamins and antibiotics in abating stress has been reported. Certain metal-binding agents have also been found to reduce the toxicity of neomycin, together with its therapeutic potential, and the author suggests that it might be possible to use radioisotopes in combination with these agents to investigate the specific action of the drugs on the labyrinthine structures.

[In the same issue of this journal (p. 398) Naunton and Ward report 2 cases of severe ototoxicity, affecting principally the cochlea, following the use of kanamycin sulphate in the presence of damaged kidney function. In each case the vestibular loss, although severe, was not so great as the cochlear.]

F. W. Watkyn-Thomas

443. **Combined Treatment with Antibiotics and Corticosteroids.** (О комбинированном лечении антибиотиками и кортикостероидными гормонами)
I. A. Kassirskij and K. P. Ivanov. *Терапевтический Архив* [*Ter. Arh.*] **31**, 13–24, Jan., 1959.

A study of the literature concerning the use of corticosteroids in acute infections reveals a conflict of opinion, some authors holding that they diminish the resistance of the infected organism and reduce the antimicrobic activity of antibiotics, while others assert that there is a synergic effect, the hormones reducing reactivity and inflammatory processes while the antibiotics suppress the infection.

The present authors conclude from their own experience that for the treatment of certain infective processes, particularly those in which allergic phenomena predominate (such as tuberculous pleurisy), and of protracted severe sepsis (such as osteomyelitis) the combination of steroids and antibiotics is superior to the use of antibiotics alone. Indeed, several cases are cited in which complete control was not attained until antibiotic treatment was supplemented with cortisone or corticotrophin (ACTH). Two illustrative cases of infective endocarditis, two of osteomyelitis, and one of cholangitis with general sepsis are described in full.

L. Firman-Edwards

444. **A Comparison of Erythromycin with Oleandomycin in Combination with Other Antibiotics against Hospital Staphylococci**
H. J. Elliott and W. H. Hall. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **53**, 364–375, March, 1959. 13 refs.

The antibacterial action of 5 antibiotic preparations of the erythromycin group—erythromycin, oleandomycin, "oleandopen" (Compound AP, oleandomycin salt of benzylpenicillin), fortified oleandopen (Compound APG, oleandopen fortified with benzylpenicillin), and "sigmamycin"—and of paired combinations of all these with bacitracin, chloramphenicol, tetracycline, benzylpenicillin, neomycin, vancomycin, and novobiocin against 30 hospital strains of coagulase-positive haemolytic *Staphylococcus aureus* has been examined at the Veterans Administration Hospital, Minneapolis, and the University of Minnesota Medical School by the methods previously described by the authors (*J. Lab. clin. Med.*, 1957, **50**, 242; *Abstr. Wld Med.*, 1958, **23**, 247).

Erythromycin and sigmamycin had the greatest bacteriostatic effect; sigmamycin was more active than either of its two components, oleandomycin and tetracycline. The oleandomycin–penicillin mixtures were slightly more active than oleandomycin and much more active than benzylpenicillin against the strains tested, which were predominantly penicillin-resistant. Erythromycin had the greatest and oleandomycin the least bactericidal action. Cross-resistance to oleandomycin was frequently found in erythromycin-resistant staphylococci, but the reverse finding was unusual. Additive potentiation of the bacteriostatic activity of oleandomycin and Compounds AP and APG occurred most frequently with bacitracin, chloramphenicol, erythromycin, and other oleandomycin mixtures. Potentiation of their bactericidal activity was unusual with neomycin, while tetracycline was less effective in increasing their bactericidal action than in enhancing bacteriostasis.

None of the antibiotic combinations studied showed true synergism. Antagonism in respect of bacteriostatic activity was rare, but antagonism in respect of bactericidal activity occurred more frequently, particularly with certain susceptible organisms, one-third of the strains tested accounting for 82% of the instances of antagonism.

J. E. Page

445. **Antibacterial Activity of Serum of Normal Men after Oral Doses of Erythromycin Propionate and Triacetyloleandomycin**
H. A. Hirsch, C. M. Kunin, and M. Finland. *New England Journal of Medicine* [*New Engl. J. Med.*] **260**, 408–412, Feb. 26, 1959. 2 figs., 7 refs.

In this study, reported from the Thorndyke Memorial Laboratory (Harvard Medical School), Boston, the antistreptococcal and antistaphylococcal activity of the serum of 8 healthy young men was assayed by a twofold dilution method 1, 2, 4, 8, 12, and 25 hours after a single dose of erythromycin monopropionate or triacetyloleandomycin equivalent to 500 mg. of the base of each drug. In addition, the concentration of each antibiotic in the serum was determined by standard methods of antibiotic assay, the results being expressed numerically in terms of "activity equivalents" for both drugs by comparison with standard solutions of their respective bases.

It was shown that antistreptococcal and antistaphylococcal activity of the serum at each interval, as also the peak activity and "total" activity, as judged from the maximum inhibiting dilutions of the sera, were several times greater after erythromycin propionate than after triacetyloleandomycin, the maximum antistreptococcal activity after erythromycin being 24 times and the antistaphylococcal being 8 times the maximum activity after oleandomycin. On the other hand the mean concentrations of oleandomycin at 1, 2, and 4 hours after the dose of triacetyloleandomycin were slightly greater than the corresponding concentrations of erythromycin, but the reverse was true at subsequent intervals after the dose, and the total activity in the serum in terms of the homologous antibiotic was the same. In discussion the authors stress the importance of differentiating between the amount of antibacterial activity produced by antibiotics in the serum and the levels of such antibiotics that can be determined in the serum. In comparing different antibiotics for their relative therapeutic value only the former is significant, whereas the latter may sometimes be grossly misleading.

A. J. Karlish

Tuberculosis

446. **Freeze Dried BCG Vaccination of Newborn Infants by the Multiple Puncture Method**
J. LORBER. *Tubercle* [*Tubercle* (*Lond.*)] **40**, 21–25, Feb., 1959. 1 fig., 17 refs.

The intracutaneous injection of B.C.G. in infants leads in about 5% of cases to troublesome ulcers or lymphadenitis. To avoid these complications a percutaneous method has been developed in the Department of Child Health of the University of Sheffield in which British freeze-dried B.C.G. mixed with a solution of dextran to form a sticky fluid about 50 times stronger than the intradermal solution is used. Vaccination is performed over the insertion of the left deltoid muscle with a Heaf multiple-puncture gun, two insertions of the needles being made through a drop of vaccine, the second after slight rotation. Of 240 infants vaccinated by this method, 95·8% gave a positive reaction at 6 to 8 weeks to a patch test with tuberculin jelly or to the Heaf or Mantoux test, this proportion increasing to 97·5% at 4 months. The lesions consisted of 4 to 12 papules, no ulceration, suppuration, or enlargement of the lymph nodes being observed. The duration of allergy after this procedure is at present unknown, and it will be necessary to follow up this group, and others, for several years before a final conclusion as to its efficacy can be reached. *Arnold Pines*

447. **Cycloserine in Tuberculosis in Children.** (La cyclosérine dans la tuberculose de l'enfant)
A. BRETON, B. GAUDIER, and C. PONTÉ. *Archives françaises de pédiatrie* [*Arch. franç. Pédiat.*] **15**, 1322–1348, 1958. 13 figs., bibliography.

Cycloserine inhibits the growth of some two-thirds of strains of tubercle bacilli *in vitro*, but its action is only of moderate intensity and a concentration of 1 to 10 μg. per ml. is required to obtain this effect. The sensitivity of tubercle bacilli to cycloserine is independent of that to other antibiotics, and no synergy has been demonstrated. Resistance develops rapidly *in vitro*. In experimental animals the therapeutic activity of cycloserine is slight, partly because it is rapidly eliminated from the body, and partly because the serum of certain animals inhibits its action. In man the excretion of the drug is similarly rapid, but it diffuses readily into the various tissues and body fluids.

In the clinical trial reported in this paper 50 children with tuberculosis were treated with cycloserine in doses of 10 to 30 mg. per kg. body weight daily by mouth for one to 9 (average 5) months. Only the milder forms of childhood tuberculosis were so treated, most of the 50 being cases of primary pulmonary tuberculosis. No previous treatment had been given in 40 cases, while the remaining 10 patients had received isoniazid, with or without PAS or streptomycin, without benefit. Most of the children improved subjectively and gained weight well, and the erythrocyte sedimentation rate fell towards the normal level. Marked radiological improvement was noted in 11 cases and slight improvement in 18; there was no improvement in 14.

Tubercle bacilli were recovered at the beginning of treatment or during the first month in 15 cases, of which only one remained bacteriologically positive after 3 months. The only serious toxic reactions observed were convulsions in 2 cases, but behaviour disorders were common. A variety of electroencephalographic abnormalities were detected during treatment, but most of these were not associated with clinical signs or symptoms.

[An enthusiastic but uncritical report, without consideration of the benign nature of the conditions which were treated and without any controls or comparison with other methods of management. The patients underwent a vast amount of investigation which was of little value. On the evidence provided cycloserine would seem to be toxic and ineffective.] *John Lorber*

RESPIRATORY TUBERCULOSIS

448. **Endocavitary Aspiration (Monaldi) in the Treatment of Pulmonary Tuberculosis.** (L'aspirazione endocavitaria di Monaldi nel trattamento della tubercolosi polmonare)
M. A. SISTI and G. U. MESSINA. *Archivio di tisiologia e delle malattie dell'apparato respiratorio* [*Arch. Tisiol.*] **14**, 50–67, Jan., 1959. 5 figs., 40 refs.

The results of endocavitary aspiration carried out by Monaldi's technique in 106 cases of pulmonary tuberculosis during the period 1950–6 are reported from the Ospedale Sanatoriale " D. Cotugno ", Bari. The treatment was given for 2 to 18 (average 6) months, and was preceded in every case by chemotherapy, usually of one year's duration. Endocavitary aspiration was the only surgical procedure adopted in 20 of the 106 cases, and in all of these resolution and complete closure of the cavity was accomplished. The remaining 86 patients, whose disease was more extensive and generally of long standing, also underwent various forms of thoracoplasty, with ultimate arrest of the tuberculosis in 81 cases. Four representative cases are described and illustrated with radiographs. The complications were few and none were serious. In about 20% of cases cavities reopened after an average interval of 2 years, but final closure of these reopened cavities occurred after a further period of aspiration varying from 2 to 4 months.

It is the authors' conviction that this method results in a considerable saving in duration of treatment, with conservation of valuable pulmonary function in many chronic and extensive cases of tuberculosis.

A. J. Karlish

449. **Segmental Resection for Pulmonary Tuberculosis. An Analysis of 335 Cases**
V. O. BJÖRK. *Journal of Thoracic Surgery* [*J. thorac. Surg.*] **37**, 135–147, Feb., 1959. 9 figs., 3 refs.

An analysis is made of 335 cases of segmental resection for pulmonary tuberculosis. The operative mortality (including patients with marked ventilatory insufficiency) was 1·5%. Of the 170 patients followed from 1 to 6 years, it has been gratifying to find 97% with a negative direct smear and 94% with a negative culture and guinea pig test of sputum and gastric washings. Ninety-two per cent. were working full time. The incidence of impaired arm movements, pain, cough, and dyspnea is recorded. The best cosmetic result and best arm movements were obtained when no thoracoplasty was added. The diaphragm mobilization gave the best cosmetic but the worst functional result of the different space-diminishing procedures. The osteoplastic thoracoplasty gave a better cosmetic result and better arm movements when compared with a thoracoplasty with rib resection. There was a higher incidence of postoperative pain in the group in which rib resection thoracoplasty was performed. The late functional result has been very encouraging and it has been proved that segmental resections can be performed with a minimal loss of function. The contralateral side has withstood the resection very well.—[Author's summary.]

450. **An Analysis of the Pulmonary Function of Ninety Patients following Pneumonectomy for Pulmonary Tuberculosis**
G. J. TAMMELING and C. D. LAROS. *Journal of Thoracic Surgery* [*J. thorac. Surg.*] **37**, 148–165, Feb., 1959. 8 figs., 21 refs.

A comprehensive study is presented of the pulmonary function of 90 patients 29 to 84 (mean 52) months after pneumonectomy for tuberculosis. The most important fact emerging from this study is that the authors found that in their cases a space-filling thoracoplasty, performed either at the time of resection or later, does nothing to prevent distension of the remaining lung and has, moreover, an unfavourable effect on the patient's ultimate lung function. *A. M. Macarthur*

451. **Observations on Ambulatory Tuberculous Patients with Pulmonary Cavities and Noninfectious Sputum (the "Open-negative" Syndrome)**
J. BREUER, H. ABELES, A. D. CHAVES, and A. B. ROBINS. *American Review of Tuberculosis and Pulmonary Diseases* [*Amer. Rev. Tuberc.*] **78**, 725–734, Nov., 1958. 7 refs.

The authors, writing from the Bureau of Tuberculosis, New York City Department of Health, describe the subsequent fate of 94 patients with persistent cavitation and negative sputum after treatment for pulmonary tuberculosis. The radiological appearances had been stable for at least 6 months in all cases before admission to the present study. All the patients had had at least 6 months' chemotherapy, and 56 were still receiving drug treatment at the close of the study. Despite this, reactivation occurred in 10 patients (11%), more commonly in those with small (under 5 cm.), thick-walled cavities. Fluid levels, bullae, and thin-walled cavities were not commonly associated with reactivation. The drug regimens [not detailed] varied greatly, but always included isoniazid.

[No information is given concerning drug resistance, which probably accounted for most of the cases of reactivation. With effective and rigorously controlled modern drug regimens the persistence of cavities has been shown by Ross *et al.* (*Brit. med. J.*, 1958, **1**, 237; *Abstr. Wld Med.*, 1958, **24**, 98) to have little influence upon the subsequent fate of patients with pulmonary tuberculosis. Provided that at least 18 to 24 months of continuous chemotherapy is given, relapse is very rare if the organisms are initially sensitive to at least 2 of the 3 major antituberculous drugs.] *Arnold Pines*

452. **Transient Rounded Lesions following Tuberculous Pleural Effusion in Children**
L. H. CAPEL and W. F. RICHARDS. *Tubercle* [*Tubercle (Lond.)*] **39**, 388–393, Dec., 1958. 4 figs., 6 refs.

The authors describe the radiological appearances of the rounded lesions which occasionally appear in children with tuberculous pleural effusion. In 21 patients out of a total of 211 cases of pleural effusion admitted to High Wood Hospital, Brentwood, Essex, in the period 1953–7 27 such lesions were observed. The lesions were demonstrable either on the antero-posterior or lateral projections or on tomography. Of the 21 patients, 17 received chemotherapy and the period of follow-up averaged 2¼ years.

Most of the lesions developed within 5 months of the onset of the effusion, which had resolved or was resolving when they were first noted. Most were shown to be in contact with the edge of residual fluid and 21 were considered to be definitely in the pleural cavity. They occurred in any zone and disappeared gradually over a period of one to 6 (average 2) months. In some a calcified fleck was left at the site of the lesion. The authors consider the lesions to be due to loculated effusion contained by adhesions from a previous pleurisy and to have no particular significance either in treatment or prognosis. They agree nevertheless that the possibility that some of these lesions are due to a perifocal pneumonia, as suggested by Canetti, cannot be excluded. *L. Capper*

453. **Adrenocorticosteroids in the Treatment of Tuberculosis**
H. J. WEINSTEIN and J. J. KOLER. *New England Journal of Medicine* [*New Engl. J. Med.*] **260**, 412–417, Feb. 26, 1959. 2 figs., 8 refs.

Adrenal corticosteroids have been used as an adjuvant in the treatment of tuberculosis at Firland Sanatorium, Seattle, since 1954. In 1956 a controlled study was begun in which 100 adult patients suffering from pulmonary tuberculosis and selected on various stated grounds from a total of 270 consecutive patients on admission were allocated on a statistically predetermined random basis to one of two groups, those in Group 1 receiving standard antituberculous treatment consisting of isoniazid and PAS, while those in Group 2 were given prednisolone in diminishing doses, beginning with 20 mg. daily for

10 days, for a total of 68 days in addition to the standard regimen.

In the authors' view patients in the steroid-treated group derived definite advantages, as shown by their shorter duration of stay in hospital, accelerated sputum conversion, and particularly by earlier cavity closure. No detrimental effects attributable to prednisolone were observed.

[It is not easy to draw definite conclusions from the results presented. The dosage of prednisolone would probably be considered inadequate and is well below that adopted in similar studies carried out in Great Britain in which clear-cut advantages were demonstrated, particularly in highly active cases of the disease.]

A. J. Karlish

454. **A Five-year Assessment of Patients in a Controlled Trial of Streptomycin with Different Doses of *para*-Aminosalicylic Acid in Pulmonary Tuberculosis. Report to the Tuberculosis Chemotherapy Trials Committee of the Medical Research Council**

W. Fox and I. Sutherland. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **28**, 77–95, Jan., 1959. 1 fig., 8 refs.

This paper presents a detailed 5-year follow-up of the 115 patients included in the Medical Research Council's third controlled trial of streptomycin and PAS in the treatment of pulmonary tuberculosis. The patients were young adults with acute bilateral progressive pulmonary tuberculosis of recent origin who were treated in hospital for 6 months. They were divided into three series at random, each of which received a 3-month course of chemotherapy consisting of streptomycin in combination with PAS. The dose of streptomycin was 1 g. daily in all three series, while that of PAS was 20 g. daily in Series S.P. 20, 10 g. daily in Series S.P. 10, and 5 g. daily in Series S.P. 5. At the end of the 3 months the clinician in charge of each case was free to institute other treatment if necessary, but adhered to the same dosage schedule whenever possible. On entry to the trial there were rather more seriously ill patients in Series S.P. 10 than in the others and the subsequent progress of this group was less favourable, but otherwise there was little clinical or radiological difference between the groups.

The 5-year survival rate was 81% in Series S.P. 20, 74% in Series S.P. 10, and 79% in Series S.P. 5. At the end of the 5 years the proportions of patients in the three series with quiescent or arrested disease were 66%, 45%, and 52% respectively. By the end of the first 3 months 15% of Series S.P. 20, 35% of Series S.P. 10, and 52% of Series S.P. 5 had developed streptomycin-resistant strains of tubercle bacillus; only 3 strains resistant to PAS were isolated.

The outcome of the disease was less favourable in patients who had extensive cavitation, high pyrexia, or a high erythrocyte sedimentation rate (E.S.R.) on admission to the trial. It was also less favourable in patients who failed to improve radiographically, who remained bacteriologically positive, or in whom the temperature or E.S.R. had failed to respond by the end of 3 months. The effect on prognosis of the development of bacterial resistance to streptomycin was less marked, though there was " some evidence of association between the outcome at five years and the presence of resistance during the first six months, among patients with the same extent of initial cavitation ". However, the extent of initial cavitation appeared to be of greater importance in the prognosis than the emergence of streptomycin-resistant organisms. The 5-year progress of the 40 patients in Series S.P. 20 was closely similar to that of the 53 patients treated in a similar way one year earlier in the second M.R.C. trial.

It is pointed out that this group of patients started treatment more than 7 years ago and, judged by present standards, were inadequately treated, so that " their fate may therefore seem to be of historical interest only ". But the efficacy of more modern methods of treatment will have to be judged from the results of long-term trials, when the results of earlier series such as this will provide a useful basis for comparison.

C. M. Fletcher

455. **A Study of " Tebafen " in Chronic Pulmonary Tuberculosis**

R. J. Cuthbert, A. M. T. Drimmie, and K. R. Urquhart. *Tubercle* [*Tubercle* (*Lond.*)] **39**, 360–366, Dec., 1958. 19 refs.

In view of the importance of combined drug therapy of pulmonary tuberculosis in order to minimize the development of bacterial resistance to any one drug the authors, working at the Chest Clinic, Southern General Hospital, Glasgow, have tried the effect of " tebafen ", a combination of isoniazid and nicotinaldehyde thiosemicarbazone (TSC) in the treatment of 25 out-patients with chronic sputum-positive tuberculosis, all of whom had previously had antituberculous drug treatment in hospital. The organisms present in the sputum were sensitive to TSC in all cases, sensitive to isoniazid in 14, and partially resistant to isoniazid in 11. The dose of tebafen was 300 mg. daily; 20 of the patients completed 6 months' treatment and 10 continued for 12 months.

One patient (whose sputum had become negative) developed jaundice after 5 months, one deteriorated generally but improved when treatment was stopped, and in a third case nausea and vomiting necessitated cessation of therapy. Subjective improvement was reported by 21 patients, but radiological improvement was seen in only 3, and only 6 patients became sputum-negative after periods of treatment varying from 2 to 12 months. Complete resistance to isoniazid developed in 5 patients and partial resistance in 4. The authors, pointing out that these were all chronic cases and that therefore startling results were not to be expected, suggest that in patients intolerant of streptomycin or PAS the use of tebafen is preferable to that of isoniazid alone or to the more expensive combinations containing cycloserine or pyrazinamide. Tebafen has the advantages of greater palatability, smaller tablet size, and smaller daily dosage. It does not cause gastric irritation and is therefore likely to be taken more willingly by the patient.

L. Capper

Venereal Diseases

456. **Tetracycline Phosphate Complex in the Treatment of Acute Gonococcal Urethritis in Men**
M. MARMELL and A. PRIGOT. *Antibiotic Medicine and Clinical Therapy* [*Antibiot. Med.*] **6**, 108–110, Feb., 1959. 4 refs.

In this study the authors have investigated, at the Venereal Diseases Clinic of the Harlem Hospital, New York, the efficacy of the phosphate complex salt of tetracycline, which is stated to be absorbed more rapidly and efficiently than the hydrochloride on oral administration, in the treatment of 113 male patients with acute gonococcal urethritis. Three treatment schedules were employed, 27 men receiving 0·75 g. divided in three doses of 250 mg. each, 52 a total of 1·0 g. in four doses, and 34 being given 1·5 g. in three doses each of 500 mg., the whole of each dose being given in one day. The criterion of cure was the finding of a negative smear and culture on two occasions during an observation period of not less than 6 days after treatment.

In the group receiving 0·75 g. there were 4 failures among the 20 followed up (80% cured). Among 36 receiving 1 g. there were 4 failures, but 2 of these may have been re-infections (94·4% cure), while of the 18 cases followed up after receiving 1·5 g., all were cured. No side-effects were noted in any case. These results correspond closely with the authors' previous series treated with tetracycline hydrochloride, in which the cure rate was 90%. It is concluded that 1 g. of the phosphate complex is the minimum effective dose.

Douglas J. Campbell

457. **Tetracycline with Glucosamine in the Treatment of Gonorrhea in the Male**
M. MARMELL and A. PRIGOT. *Antibiotic Medicine and Clinical Therapy* [*Antibiot. Med.*] **6**, 117–119, Feb., 1959. 7 refs.

In view of the report by Welch *et al.* (*Antibiot. Med.*, 1958, **5**, 52) and other workers that the addition of glucosamine to tetracycline produces higher serum concentrations of the antibiotic than does tetracycline alone, the authors have tried this new medication in the treatment of 101 cases of acute gonococcal urethritis in men attending the Venereal Diseases Clinic, Harlem Hospital, New York.

Of the 81 cases adequately followed, among 8 who had received 500 mg. of the drug in one day there were 2 failures, among 26 receiving 750 mg. there were 5 failures, among 35 given 1,000 mg. there were 2 failures, while among 12 who received 1,500 mg. there were no failures. Thus a dosage of at least 1 g. produced a cure rate of over 94%, a rate comparable to that achieved with 1·5 g. of tetracycline hydrochloride in the authors' previous series reviewed in 1954 [and also similar to the results obtained by the same authors with 1 g. of the tetracycline phosphate complex (see Abstract 456)]. As they point out, a decrease of one-third in the small doses of antibiotic required to cure gonorrhoea in the male may not appear to be of much significance, but does assume economic importance in a clinic where hundreds of cases are treated annually.

Douglas J. Campbell

458. **The Use of Tetracycline Phosphate Complex in a Venereal Disease Clinic**
M. MARMELL and A. PRIGOT. *Antibiotic Medicine and Clinical Therapy* [*Antibiot. Med.*] **6**, 111–116, Feb., 1959. 2 figs., 4 refs.

At the Venereal Diseases Clinic of Harlem Hospital, New York, the authors had found the tetracycline phosphate complex to be efficacious in the treatment of acute gonococcal urethritis in the male [see Abstract 456]. They have now used this same drug to treat other types of case referred to the clinic.

Whereas 1 g. of the complex cured over 90% of cases of acute gonococcal urethritis, in the present series one case of donovanosis required 39 g. of the drug, one of chancroid required 14 g., while 8 cases of lymphogranuloma, all showing inguinal adenopathy and all but one a positive result in the Frei test, required from 7 to 24 g. One case of staphylococcal scrotal abscess, with a positive reaction to the Frei and complement-fixation tests, responded to 6 g. (The authors do not use the term "cure" for these cases but prefer "healing".) They observed no allergic or toxic reactions in any of the present cases, and conclude that the tetracycline phosphate complex can be successfully employed in the treatment of various infections, other than syphilis, encountered in a venereal diseases clinic.

Douglas J. Campbell

SYPHILIS

459. **Spirochaetal Agglutination in the Cerebrospinal Fluid.** (Die Spirochätenagglutination im Liquor)
H. G. GRAM. *Deutsche medizinische Wochenschrift* [*Dtsch. med. Wschr.*] **84**, 109–112, Jan. 16, 1959. 32 refs.

In this paper from the Municipal Hospital, Karlsruhe, a spirochaetal agglutination (S.A.) test developed on the basis of observations made by Hoffman and Prowazek in 1906 is described and the results obtained with cerebrospinal fluid (C.S.F.) are compared with those of the Wasserman and Meinicke reactions and complement-fixation tests with citochol and cardiolipin antigens. It is stated that although the result of the S.A. test is usually related to the globulin content of the fluid, the relationship does not appear to be so close as that encountered, for instance, in the Wasserman reaction. The active antigen seems to be a specific treponemal protein. [For details of the technique the original paper should be consulted.]

In 658 of the 740 cases in which the tests were performed in parallel the result of the S.A. test was in complete agreement with those of the other tests used (621 negative, 37 positive). In 82 cases discordant results were obtained with the different tests, but those of the S.A. test gave the highest degree of correlation with the clinical diagnosis. The S.A. test gave a false positive result in only 6 cases, 3 of which were among the 10 cases of bacterial or viral meningitis tested, in which the globulin level of the C.S.F. was increased, and one a case of cirrhosis. One false negative result was noted.

It is considered that the simplicity of the method commends it for more general use. *Allene Scott*

460. **V.D.R.L., Eagle, Price, and Kolmer Tests—a Comparison Using 1,029 South African Bantu Sera**
S. B. GRIFFITHS, G. C. BUCKLE, and J. W. HILL. *British Journal of Venereal Diseases* [*Brit. J. vener. Dis.*] **35**, 40–43, March, 1959. 1 fig., 6 refs.

A comprehensive evaluation of serological tests for syphilis in the various racial groups of South Africa has been initiated by the Natal Provincial Pathological Service, and in this paper from the University of Natal the results are presented of tests carried out on an unselected series of young, apparently healthy, Bantu males. The techniques used were the Eagle flocculation test, the V.D.R.L. slide test, the Kolmer complement-fixation test, and the Price precipitation reaction.

Of the 1,029 sera tested, 151 (14·7%) reacted to one or more of the tests. There were 122 reactors to the V.D.R.L. test, 124 to the Eagle test, 75 to the Price test, and 87 to the Kolmer test. Only 57 (37·7%) of the 151 reacted to all four tests, whereas 38 (25·2%) reacted to only one, which in 29 cases was one of the flocculation tests (V.D.R.L. or Eagle). It is considered unlikely that the large proportion of reactors was due to a high incidence of syphilis, and more probably that it was due to non-specific factors. There was a large degree of disagreement between the results obtained by the different tests.

The authors suggest that different racial groups, because of their different antigenic experiences, would be expected to react differently to the same serological test. In such circumstances each serological test for syphilis should be evaluated for the racial group in which it is to be used, as estimates of sensitivity and specificity which are applicable to one racial group do not necessarily apply to another. *R. R. Willcox*

461. **A Note on the Course of Reagin Titres in Chronic Biologic False Positive Reactors**
J. ENG. *British Journal of Venereal Diseases* [*Brit. J. vener. Dis.*] **35**, 44–46, March, 1959. 1 fig., 4 refs.

Changes in the titre of the Wassermann reaction (W.R.) and the Meinicke clarification reaction (M.K.R.) in 11 patients in whom positive serological reactions for syphilis had been observed for 2 years or more (although the treponemal immobilization reaction had been negative on one or more occasions), and in whom there were no clinical signs or history of syphilis were studied over a period of 2 to 8 years at the State Institute of Public Health, Oslo. In 3 patients, all of whom were among those observed for the longest time (8, 8, and 7 years respectively), the M.K.R. titre increased steadily during the period in spite of earlier anti-syphilitic treatment. Only one of these 3 showed a definite increase in the W.R. titre. None of the other patients, 3 of whom had received anti-syphilitic treatment, showed an increase in either titre.

The reported relationship between biological false positive reactions and the collagen diseases is noted. A clinical diagnosis was made in 5 of the 11 patients, namely, (1) chronic cystopyelonephritis with anaemia, (2) rheumatoid arthritis and suspected disseminated lupus erythematosus, (3) circulatory failure, vascular hypertension, and crural ulcers, (4) psychosis, and (5) peptic ulcer. Increasing M.K.R. titres were observed in Cases 1 and 2. *R. R. Willcox*

462. **The Prognosis in Syphilitic Aortic Aneurysm after Treatment with Penicillin**
R. WARD and L. READ. *British Journal of Diseases of the Chest* [*Brit. J. Dis. Chest*] **53**, 52–56, Jan., 1959. 4 figs., 11 refs.

This paper from Blackburn Royal Infirmary, Lancashire, deals with 13 cases of syphilitic aortic aneurysm occurring in 7 women and 6 men aged between 55 and 73 years which were treated solely with penicillin. The periods of observation after treatment varied between 20 and 74 months. In 9 cases the aneurysm was sacular and in 4 fusiform, and in all cases serological tests for syphilis were positive. When first seen the patients were already symptomatic, pain, dysphagia, and hoarseness being the most common complaints, but nevertheless the diagnosis was always confirmed radiologically. It is of interest that 2 patients showed signs of obstruction of the superior vena cava, 4 of aortic incompetence, and 3 of concomitant neurosyphilis. No patient had previously received any treatment and, though a few of the earlier cases were given full doses of potassium iodide for 3 weeks before starting penicillin treatment, this practice was soon abandoned. Each patient received 600,000 units of procaine penicillin daily to a total of 20 million units, but no patient was re-treated. A Herxheimer reaction with hypotension and associated weakness occurred in 2 patients, but both recovered in a few hours.

Of the 13 patients 3 died during the follow-up period, but in no case was death due to rupture of the aneurysm; 2 of these patients were by then aged 70 and 74 respectively and the third, aged 55 and who also had aortic incompetence, died from bronchopneumonia 4 years after treatment. Of the remaining 10, 9 are leading nearly normal lives and symptoms have mostly disappeared. The authors conclude that penicillin relieves many symptoms caused by syphilitic aortic aneurysm. In view of the fact that all the patients treated had definite symptoms indicating that death might occur within one or 2 years, they suggest that surgery will have no further part to play in the treatment of this condition. *G. L. M. McElligott*

Tropical Medicine

463. **The Effects of Kwashiorkor on the Development of the Bones of the Knee**
P. R. M. JONES and R. F. A. DEAN. *Journal of Pediatrics* [*J. Pediat.*] **54**, 176–184, Feb., 1959. 4 figs., 4 refs.

Evidence of retardation of bone growth in kwashiorkor, found by radiological examination of the bones of the hand, has previously been presented by the authors (*J. trop. Pediat.*, 1956, **2**, 51), the bones of children with kwashiorkor being smaller and less well calcified and showing a less pronounced trabecular pattern than those of normal children. In the present paper they describe similar changes which have been seen in the knees of 44 African boys and 31 girls with kwashiorkor examined at Mulago Hospital, Kampala, Uganda. Moreover, transverse lines indicating past disturbances of bone growth were found more frequently in the femur and tibia than in the bones of the hand and wrist, and it is suggested that the knee may be a more accurate indicator of retardation of bone development than the hand. *R. Schneider*

464. **Clinical Aspects of Tropical Ataxic Neuropathies Related to Malnutrition**
G. L. MONEY. *West African Medical Journal* [*W. Afr. med. J.*] **8**, 3–17, Feb., 1959. 34 refs.

The author has studied at University College Hospital, Ibadan, Nigeria, 100 cases of ataxic neuropathy of nutritional origin occurring in 60 males and 40 females aged 11 to 70 years, the maximum incidence (49 cases) being between 31 and 50 years. A history of similar disorders in housemates or relatives was obtained in 41 cases; it appeared that sharing the same cooking pot was of greater aetiological importance than blood relationship. A history of repeated attacks of mucocutaneous lesions, such as angular stomatitis, glossitis, and genital eczema, was elicited in 96% of cases and active lesions of this type were observed in a total of 74 patients.

Subjective sensory disturbances included "burning feet", pains in the limbs, and paraesthesiae. Objectively, loss of sense of position in the lower limbs was demonstrated in 82% of cases. Motor weakness was noted in only 8 cases, but some degree of ataxia was present in every case, the gait in 75 cases being frankly ataxic, and 3 of these patients were paraplegic. Loss of sphincter control was not observed. A history of defective vision was elicited in 87 cases and there was temporal pallor of the optic disks in 25. Blood counts and examination of the urine and fasting gastric juice all yielded normal findings. The Kahn test gave a negative result in 21 out of 22 cases examined. The cerebrospinal fluid, examined in 20 cases, was normal in all except possibly for a raised protein content in 5. Dietary treatment, with added supplements of the vitamin-B complex orally and by injection, cleared up the symptoms in early cases, but did not affect long-standing cases. Discussing the aetiology of the condition, the author considers that it is most probably due to some nutritional deficiency, but a toxic factor cannot be ruled out. *William Hughes*

INFECTIOUS DISEASES

465. **The Protection against Trypanosomiasis Conferred on Cattle by Repeated Doses of Antrycide, Alone or with *Trypanosoma congolense***
I. M. SMITH. *Annals of Tropical Medicine and Parasitology* [*Ann. trop. Med. Parasit.*] **52**, 391–401, Dec., 1958. 1 fig., 14 refs.

This paper from the East African Trypanosomiasis Research Organization, Tororo, Uganda, describes an experiment designed to confirm and extend the observation of Soltys (*Ann. trop. Med. Parasit.*, 1955, **49**, 1) that when animals are given a prophylactic course of "antrycide" (quinapyramine) they will, in the presence of infection, develop a resistance to the strain of *Trypanosoma congolense* of the area in which they are living.

The standard mixture of quinapyramine sulphate and chloride was used and was injected as a 10% suspension in distilled water into the dewlap of short-horned Zebu cattle in doses of 5 mg. per kg. body weight. Immunizing and challenging inocula were prepared from the heart blood of rats heavily infected with a strain of *T. congolense* isolated from a naturally infected rat and maintained in guinea-pigs by cyclical transmission by *Glossina pallipides* or *G. mortisans*. The cattle were divided at random into four groups of 6 animals. Group A were dosed with the drug, and one week later were given a subcutaneous injection of 2 million trypanosomes; this procedure was repeated 6 times at 2-monthly intervals, the immunizing dose varying from 64 million to 154 million organisms. Group B were similarly treated with quinapyramine, but no trypanosomes were injected. Group C received neither drug nor trypanosomes. Group D was divided into three lots of 2 animals which were inoculated at the beginning, middle, and end of the period of experimental treatment respectively to demonstrate the virulence of the organism. A challenge dose of 4 million organisms was administered to Groups A, B, and C five times at monthly intervals, starting 6 months after the end of the treatment period. This inoculum was equivalent to about 16 times the 50% effective dose for Zebu cattle.

All the animals in Group A and 4 of those in Group B resisted the test inocula, which readily infected Group C. About 80 days after the fifth challenge drug-fast *T. congolense* were persistently found in the peripheral blood of 2 animals of Group B. The results of serological examinations were inconclusive. *I. M. Rollo*

466. **Pyrimethamine Resistance in *Plasmodium vivax* Malaria**

M. D. YOUNG and R. W. BURGESS. *Bulletin of the World Health Organization* [*Bull. Wld Hlth Org.*] **20**, 27–36, 1959. 2 figs., 5 refs.

P. vivax infection (Korean, St. Elizabeth or Chesson strain) was induced in 17 neurosyphilitic patients. Pyrimethamine in single doses of either 25, 50, 100 or 200 mg. was given to test the schizontocidal and sporontocidal effects. The first single-dose treatment of 25 mg. or 100 mg. was given between the 8th and 61st days of parasite patency and gave moderately rapid schizontocidal and very rapid sporontocidal effects. All observed cases relapsed. The second treatment, usually 3 weeks or longer after the first and with the same or higher doses, had either a diminished effect or none on the schizogonous and sporogonous cycles. Subsequent treatment, even at weekly intervals, had no effect.

The resistant quality was undiminished in subsequent infections transmitted by mosquito bites, by the injection of preserved sporozoites, or by transfusion of infected blood. Preserving sporozoites or erythrocytic parasites at very low temperatures did not materially affect the resistant quality.

In view of the evidence presented, it appears that resistance could also occur in the field when large single doses of pyrimethamine alone are given at less than monthly intervals to febrile persons having active *P. vivax* infections.—[Authors' summary.]

467. **Suramin Complexes. IV. Ethidium Bromide Complex: a Large-scale Laboratory Trial of Its Prophylactic Activity in Cattle**

L. E. STEPHEN. *Annals of Tropical Medicine and Parasitology* [*Ann. trop. Med. Parasit.*] **52**, 417–426, Dec., 1958. 2 figs., 6 refs.

The prophylactic properties of ethidium-bromide–suramin complex against animal trypanosomiasis were tested at the West African Institute for Trypanosomiasis, Vom, Northern Nigeria on Zebu cattle, the drug being injected subcutaneously into three groups of 8 animals in doses of 10, 7·5, and 5 mg. per kg. body weight respectively. The combining proportion used was 0·6 part of suramin to one of ethidium bromide, with a concentration of 1 g. of ethidium bromide in 20 ml. of the complex, which was prepared fresh on the day of injection. A further group of 8 animals treated with "antrycide" (quinapyramine) pro-salt (11·7 mg. per kg.) were used as drug controls. The injections were given into the right side of the neck at a point 9 inches (23 cm.) anterior to the spine of the scapula and 4 inches (10 cm.) ventral to the ligamentum nuchae. Great care was taken to ensure that the drug was deposited in the loose subcutaneous connective tissue. The fly challenge was predominantly with wild *Glossina morsitans* and the infecting organism was principally *Trypanosoma vivax*, although *T. congolense* was also present.

With all doses of the complex severe swellings developed at the injection site which burst and mostly sloughed; in both cases most of the drug was lost. The dermo-necrotic properties of the complex appeared to be due to the ethidium bromide component and could not be correlated with age, sex, hair colour, or skin thickness of the treated animals. In 2 cases no loss of drug occurred; one animal, which received 10 mg. per kg., was protected for 10 months and the other, which received 7·5 mg. per kg., was protected for 16 months. There were no symptoms of general toxicity to adult cattle in any of the group, but all the doses used appeared to have a deleterious effect on calves.

The trypanosomes which broke through during the trial were mainly *T. congolense*, suggesting that this trypanosome is more resistant to the complex than *T. vivax*.

I. M. Rollo

468. **A Pilot Scheme to Eradicate Bancroftian Filariasis with Diethylcarbamazine. Results of the First Year's Treatment**

P. JORDAN. *Transactions of the Royal Society of Tropical Medicine and Hygiene* [*Trans. roy. Soc. trop. Med. Hyg.*] **53**, 54–60, Jan., 1959. 16 refs.

The author describes, from the East African Medical Research Institute, Mwanza, Tanganyika, a pilot scheme undertaken in an effort to eradicate Bancroftian filariasis by means of diethylcarbamazine. The site chosen for the experiment was a strip on the north-eastern shores of the island of Ukara in Lake Victoria, an island which is 6 miles square and has an unusually dense population of about 20,000. *Anopheles gambiae* abounds, so that in the rainy season anyone may get up to 200 bites in a night, and in some villages 5% of the inhabitants have elephantiasis. Various doses of diethylcarbamazine were given to the whole population of the area at either monthly or 2-monthly intervals.

It was found that a single monthly dose of 200 mg. reduced the number of cases showing microfilariae in the night blood to 19·7% of the original figure, while a dose of 200 mg. every 2 months reduced it to 39%. The results were shown to vary according to the density of microfilariae in the blood, patients with counts of 50 or over per thick drop of blood requiring larger doses of the drug than those with lower counts. It is believed that the "hard core" of remaining positive cases could maintain transmission of the disease, and further experiments with doses of 400 to 600 mg. are proposed.

Clement C. Chesterman

469. **Diethyl Dithio*iso*phthalate in the Treatment of Leprosy (ETIP or "Etisul"); a Progress Report**

T. F. DAVEY and L. M. HOGERZEIL. *Leprosy Review* [*Leprosy Rev.*] **30**, 61–72, Jan., 1959. 2 figs., 6 refs.

A report is presented from the Leprosy Service Research Unit, Uzuakoli, E. Nigeria, on the use of diethyl dithio*iso*phthalate (ETIP; "etisul") in the treatment of leprosy. This compound is the *iso*phthalic ester of ethyl mercaptan. It has a disagreeable odour which can be detected in the patient's breath 15 minutes after parenteral injection. This odour detracts from the value of the drug as, although the patient tolerates it for a while, he objects to it more and more as time goes on.

The first trial was carried out on a group of 8 cases of lepromatous and 9 of tuberculoid leprosy. The pre-

paration was administered in a dosage of 3 ml. of a 70% cream rubbed in vigorously over a wide area of the body once daily. The patients found the odour so disagreeable that the trial had to be discontinued in the fourth month. Nevertheless, even in this short period some very good results were obtained. In estimating progress the authors use a "bacterial index" (B.I.) based on the average of findings in stained smears from multiple sites, so that graphs showing changes in the B.I. with treatment can be compared with a standard graph based on the results obtained with DDS over a number of years. The graph showing the average progress of the B.I. in this first group of patients treated with ETIP fell rapidly compared with the DDS standard. In the next trial 14 patients with lepromatous and 8 with tuberculoid leprosy were treated with a similar cream to which perfume had been added in an attempt to mask the odour, 6 ml. of the cream being rubbed twice weekly into a limited area of the skin of the legs below the knees. Unfortunately, the garlic-like odour of the ETIP persisted after that of the perfume had disappeared, but the patients were persuaded to continue the treatment for periods up to 5 months. The early results were good, but the over-all results were poor. It was particularly noted in the lepromatous cases that although there was an initial rapid fall in the B.I., the curve tended to flatten out after 2 months, suggesting the development of resistance to the drug. Since it was thought that absorption of the drug from the limited area of skin used may have been defective a third trial was carried out on 10 lepromatous and 5 non-lepromatous cases in which 6 ml. of the cream was rubbed in twice weekly over a wide area for 8 to 12 weeks. These patients were studied intensively and many biopsies were taken to assess progress. There was a definite improvement, evidenced by a fall in the B.I., in the first and second months, but this was not maintained and in the third month all the patients were given DDS in addition to, or instead of, ETIP, when progress was resumed.

The authors consider that in some respects—particularly the early fall in B.I.—the response to ETIP was better than could have been achieved with any other form of treatment in their experience. Further trials are indicated, and they consider that treatment with a combination of ETIP and DDS holds out more promise than treatment with either alone. *William Hughes*

470. **Marked Increase in Mitsuda Positivity in Lepromatous Cases, with Reference to Clinical Features**
S. SATO and M. FUKUDA. *International Journal of Leprosy* [*Int. J. Leprosy*] **26**, 205–218, July–Sept., 1958 [received April, 1959]. 31 refs.

From the Research Institute for Tuberculosis and Leprosy (Tôhoku University), Sendai, Japan, the authors report a recent striking increase in the frequency of positive Mitsuda reactions in lepromatous leprosy, in which hitherto the reaction has been typically negative, and suggest that new criteria of positivity may be required. According to the criterion established at the VIth International Congress of Leprology at Madrid in 1953 a lesion of 3 mm. defines the lower limit of positivity, but the World Health Organization Expert Committee on Leprosy recommended that the lower limit should be 4 mm. Of 854 patients surveyed in 1954, 682 were lepromatous, and of these 88·3% gave a positive reaction at the 3-mm. level, 79·6% at the 4-mm. level, and 15·3% at the 7-mm. level. Of 177 of these patients re-examined in 1957, of whom 139 were lepromatous, a positive Mitsuda reaction was obtained in 86·3% at 3 mm., in 64·7% at 4 mm., and in 7·2% at 7 mm.

The authors note that in their 1954 survey they obtained positive reactions in 68·7% of 48 progressive cases and in 94·3% of 250 regressive cases, and cite other Japanese authors who have recorded similar findings in Japan. They attribute the high frequency of positive reactions mainly to sulphone therapy, but suggest that ethnic and social factors may also have had some influence, pointing out that the standard of living in Japan has been raised appreciably in recent years. They advocate that in defining a positive Mitsuda reaction in the future the lower limit should be fixed at 7 mm.
William Hughes

471. **Clinical Evaluation Studies in Lepromatous Leprosy. Third Series: Nicotinamide and BCG Vaccination as Supplements to Diaminodiphenyl Sulfone (DDS)**
J. A. DOULL, J. N. RODRIGUEZ, A. R. DAVISON, J. G. TOLENTINO, and J. V. FERNANDEZ. *International Journal of Leprosy* [*Int. J. Leprosy*] **26**, 219–235, July–Sept., 1958 [received April, 1959]. 10 refs.

The authors, working as a team simultaneously at the Eversley Childs Sanitarium and Central Luzon Sanitarium in the Philippines and the Westfort Institution, Pretoria, South Africa, have evaluated the therapeutic effect of adding nicotinamide and B.C.G. vaccination to "diasone" (DDS) in the treatment of lepromatous leprosy. At each institution the patients were allotted at random to one of two major groups, one of which was given DDS alone and the other DDS plus nicotinamide. Later the patients were divided according to whether they were tuberculin-positive or tuberculin-negative and the negative reactors allotted at random to two subgroups, one of which was given intradermal B.C.G. vaccination. All the patients were given DDS in a dosage starting with one tablet (50 mg.) every second day for the first 2 weeks and rising gradually to 4 tablets daily by the end of the 8th week. For the patients receiving nicotinamide in addition the dosage of this supplement was initially 50 mg. daily, rising to 500 mg. daily. The period of treatment lasted about 48 weeks.

At the Central Luzon Sanitarium 46% of 166 patients completing the treatment showed improvement, at the Eversley Childs Sanitarium 62% of 141 did so, and at Westfort Institution 63% of 93 patients were improved. In general it was found that clinical and bacteriological progress was much the same in each institution whichever form of therapy was used, and that B.C.G. vaccination did not improve the results. Erythema nodosum leprosum occurred with equal frequency in both groups. Only 6 of the 434 patients treated developed a positive Mitsuda reaction and this was weak in all of them.
William Hughes

Nutrition and Metabolism

472. **Serum and Tissue Concentration of Vitamin B_{12} in Certain Pathologic States**

J. A. HALSTED, J. CARROLL, and S. RUBERT. *New England Journal of Medicine* [*New Engl. J. Med.*] **260**, 575–580, March 19, 1959. 2 figs., 21 refs.

The results of microbiological assay of the serum vitamin-B_{12} (cyanocobalamin) level have been shown to be reproducible within a limit of 10% and to give a constant value for any one normal individual, although variation between individuals may be wide. Thus the mean value, as determined at the State University of New York Upstate Medical Center, for 333 healthy adults of all ages was 470 $\mu\mu$g. per ml. (S.D. 196 $\mu\mu$g.) and the range 110 to 1,260 $\mu\mu$g. per ml., there being no variation with sex or age, except that a decrease was found in a few subjects in the 10th decade.

Patients with clinical evidence of vitamin-B_{12} deficiency showed values below 104 $\mu\mu$g. per ml. [later in the paper given as 140 $\mu\mu$g. per ml.], but 93 patients with a variety of chronic disorders (including sprue, carcinoma, and hepatic disease) and degenerative neurological diseases (other than "combined-system disease") showed serum vitamin-B_{12} values within normal limits. A significantly raised serum level of the vitamin was found in patients with duodenal ulcer, diabetes with renal disease and retinopathy, and chronic myelogenous leukaemia. Determination of the vitamin store in the liver of normal subjects coming to necropsy showed that this was theoretically adequate for 1 to 6 years, with levels of approximately 50% of normal in cases in which portal cirrhosis was present. Tissue levels of the vitamin in bone marrow and intestinal mucosa were less than 1/30th of those found in the liver.

It is concluded that the findings in this study "lend no support to the contention that partial or biochemical deficiency of vitamin B_{12} may occur in various chronic diseases or old age". *F. W. Chattaway*

473. **Magnesium Depletion in Man**

R. E. RANDALL, E. C. ROSSMEISL, and K. H. BLEIFER. *Annals of Internal Medicine* [*Ann. intern. Med.*] **50**, 257–287, Feb., 1959. 3 figs., bibliography.

The signs of magnesium deficiency in animals include increased neuromuscular irritability, and a similar condition in man may sometimes be attributable to the same cause. This paper reports the findings when magnesium metabolism was investigated because of the sudden onset of mental and neuromuscular disorder in 12 patients in Boston hospitals.

The patients were 32 to 68 years old. All were severely malnourished (because of a variety of diseases) and 9 had either diarrhoea or loss of gastric contents. All but one were being fed parenterally when the symptoms suggesting magnesium deficiency developed. These included severe psychotic symptoms in 7 cases, mild confusion and disorientation in 4, twitching of muscle groups in 11, and convulsions in 2; muscle fasciculations were common, and a tremor was seen in 6 cases.

The serum magnesium level was below the normal range of 1·7 to 2·7 mEq. per litre in 10 cases, and as low as 0·4 mEq. per litre in 2. The serum calcium figures were all low, but only one patient showed latent tetany. Five had a low serum phosphorus level and 3 hypokalaemia. The urinary magnesium output was 3 mEq. or less in 24 hours in 9 cases. Magnesium sulphate (25 to 125 mEq. daily) was given parenterally to 9 patients, of whom 6 retained at least 40% in the first 3 days; high retention of dietary magnesium was found in 2 of these and 4 others. The 2 patients with a normal serum magnesium level retained 46 and 60% respectively of the magnesium given. Two patients failed to retain administered magnesium until their potassium depletion was corrected.

Parenteral magnesium therapy was followed by rapid improvement in 6 cases, while improvement occurred on a normal diet in 4. A lack of precise correlation between the serum magnesium level and the symptoms was apparent in 4 cases. Abnormal electroencephalographic findings in 6 patients improved slowly. Biopsy in 2 cases and necropsy in 6 showed no lesion comparable to those of magnesium deficiency in animals. Three cases are reported in some detail.

The authors point out that no measure of total body magnesium is yet available and that depletion of intracellular magnesium may not always be reflected in a low serum level. From a consideration of the balance data, however, they infer that their patients were suffering from magnesium depletion as a result of failure of intake and gastro-intestinal loss. They discuss the nature and site of the disturbance of function and its relation to other factors. *G. C. R. Morris*

474. **Caloric Intake in Relation to Energy Output of Obese and Non-obese Adolescent Boys**

P. A. STEFANIK, F. P. HEALD, and J. MAYER. *American Journal of Clinical Nutrition* [*Amer. J. clin. Nutr.*] **7**, 55–62, Jan.–Feb., 1959. 22 refs.

This paper from Harvard School of Public Health and the Children's Medical Center, Boston, reports a study of the average daily caloric intake and physical activity of 14 obese adolescent boys and 14 paired control subjects. Comparisons between the two groups were made during the school year and also for 8 weeks at a summer camp. The average daily food intake of a larger control group of 65 boys aged 13 to 15 was also determined.

Contrary to expectation it was found that both during the school year and in camp the mean caloric intake of the obese group was significantly less than that of the control groups. There was no discernible difference between the paired groups in the amount of time reported as

spent in active exercise, but observation suggested that the degree of enthusiasm for active sports tended to be less in the obese than in the non-obese.

It is concluded that overeating, in the sense of eating more than the average, was not typical of these obese boys, but that they probably overate in a relative sense, in that their energy expenditure was depressed below their energy intake, which was moderate for their sex and age. *A. G. Mullins*

475. **Familial Hypercholesteremic Xanthomatosis: a Preliminary Report. I. Clinical, Electrocardiographic and Laboratory Considerations**
J. L. GURAVICH. *American Journal of Medicine* [*Amer. J. Med.*] **26**, 8–29, Jan., 1959. 3 figs., 35 refs.

A preliminary report is presented of two families investigated at Lancaster Veterans Hospital, New Brunswick, Canada, in which hypercholesterolaemic xanthomatosis occurred. In all of the 103 individuals studied the serum cholesterol, cholesterol ester, lipid phosphorus, and total lipid levels were determined, and ultracentrifugal lipoprotein studies were also carried out. The results are discussed in relation to the clinical findings.

Of these 103 individuals, 41 were shown to have hypercholesterolaemia (serum cholesterol level higher than 300 mg. per 100 ml.), while a further 25 had borderline values (250 to 300 mg. per 100 ml.). Tendon, fascial, or periosteal xanthomata occurred in 23 of the 41 hypercholesterolaemic subjects, but none were seen in the borderline or normocholesterolaemic subjects; the incidence of xanthomatosis was roughly but not absolutely correlated with age. Clinically, 14 of the hypercholesterolaemic subjects showed evidence of coronary arterial disease. The incidence of hypertension and of cardiovascular and peripheral vascular disease, however, was low. *H. Harris*

476. **Studies in Essential Hypercholesterolemia and Xanthomatosis. Relationships between Age, Sex, Cholesterol Concentrations in Plasma Fractions, and Size of Tendinous Deposits**
B. HOOD and G. ANGERVALL. *American Journal of Medicine* [*Amer. J. Med.*] **26**, 30–38, Jan., 1959. 4 figs., 15 refs.

For many years the authors, working at Sahlgren's Hospital and the University, Gothenburg, Sweden, have collected data on hypercholesterolaemic xanthomatosis in a large number of patients amounting, with members of their families, to several hundred individuals. In this paper they present the results of cholesterol determinations performed on different Cohn fractions of the serum from 45 patients with xanthomatosis, 21 patients with hypercholesterolaemia but no demonstrable xanthomata, and 52 control subjects. In subjects with essential hypercholesterolaemia and xanthomatosis the elevations of the cholesterol content in Fractions I, II, and III were found to be very variable, but the cholesterol content in Fractions IV, V, and VI was below normal in these groups, except in females below the age of 50, in whom it was above normal. *H. Harris*

477. **Familial Hypercholesterolemia, Xanthomatosis and Coronary Heart Disease**
F. H. EPSTEIN, W. D. BLOCK, E. A. HAND, and T. FRANCIS. *American Journal of Medicine* [*Amer. J. Med.*] **26**, 39–53, Jan., 1959. 2 figs., 27 refs.

At the University of Michigan, Ann Arbor, the authors have reinvestigated a large kindred in which hypercholesterolaemia and xanthomatosis occurred and which was previously described by Wilkinson *et al.* (*Ann. intern. Med.*, 1948, **29**, 671; *Abstr. Wld Med.*, 1949, **6**, 55). In all, 268 individuals were studied and it was possible to estimate the serum cholesterol level in 251 of them.

The findings in this study, together with those reported in the literature, are discussed in relation to alternative genetical hypotheses which have been suggested to account for hypercholesterolaemia and xanthomatosis. For example, Wilkinson *et al.* concluded that hypercholesterolaemia is due to the presence of a single incompletely dominant gene, while xanthomatosis represents " a condition characterized by the coexistence of two such alleles ". The present authors, however, consider that the data are not fully consistent with expectation on any one of these hypotheses. They go on to suggest that greater account of possible environmental factors influencing cholesterol level will have to be taken before a satisfactory elucidation of the problem is achieved. *H. Harris*

478. **Clinical Studies with Penicillamine in Hepatolenticular Degeneration**
M. J. SEVEN, B. KLIMAN, and R. E. PETERSON. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **237**, 49–58, Jan., 1959. 3 figs., 18 refs.

Examination of the chemical nature of penicillinamine, which has a single sulphydryl group and adjacent amino and carboxyl groups, suggested that it might be usefully employed as a chelating agent in the treatment of Wilson's disease (hepatolenticular degeneration) in the same way as sodium calciumedetate (EDTA) and BAL have been used.

After extensive metabolic investigation 2 brothers, both of whom had hepatolenticular degeneration, were treated at the Clinical Center, National Institutes of Health, Bethesda, Maryland, first with EDTA and then with penicillamine. In one there was a dramatic response, both clinical and metabolic, to a 6-month intermittent course of the latter drug given in an average dosage of 2 g. daily. In the other the same treatment caused increasing anorexia and drowsiness. After interruption by an intercurrent *Salmonella* infection treatment was resumed at a lower dosage, but without clinical response. However, in this case as in the first, copper excretion was greatly increased during penicillamine therapy.

In a patient with haemochromatosis the administration of 3 g. of penicillamine resulted in only a small increase in urinary iron output, whereas excretion of copper was increased sevenfold, suggesting that penicillamine has a specific effect on copper metabolism.
Allene Scott

Gastroenterology

479. **The Too Small Mouth in Patients with " Plummer–Vinson " Syndrome**
R. J. H. KRUISINGA and E. HUIZINGA. *Annals of Otology, Rhinology and Laryngology* [*Ann. Otol. (St Louis)*] **68**, 115–121, March, 1959. 5 figs., 4 refs.

Attention is drawn in this paper from the Otolaryngological Clinic of the University of Groningen, Netherlands, to the fact that the mouths of patients with the Plummer–Vinson syndrome are often smaller than the average and that this feature gives them a highly characteristic facies. The width of the mouth may be determined in suspected cases by drawing the angles apart with two spatulae until there is discomfort and then measuring the distance between them. In 94 healthy women examined by the authors in this way the average measurement was 11 cm., whereas in 9 women in whom a firm clinical diagnosis of the Plummer–Vinson syndrome had been made the measurement ranged from 8 to 9·75 cm. It is noted that a small mouth is also found in patients with carcinoma of the upper third of the oesophagus, and that this disease is relatively more common in women in countries in which the Plummer–Vinson syndrome—predominantly a disease of women—is frequent. These facts, and others, are cited in support of the theory that there is a close relation between the two conditions. *William McKenzie*

480. **Clinical Diagnosis in Gastrointestinal Hemorrhage. A Planned Investigation Including Arteriographic Studies of the Human Stomach**
J. K. WAGSTAFF. *Gastroenterology* [*Gastroenterology*] **36**, 26–44, Jan., 1959. 4 figs., 33 refs.

A personal study of 250 cases of hematemesis or melena, planned to assess the value of symptoms and signs for determining the causal lesion, is reported. A comparison of gastric and duodenal ulcer shows that the following features were significantly more common ($P<0.05$) with either one or the other. *Gastric ulcer.* (1) Pain or discomfort occurring within ½ hour of eating; (2) anorexia; (3) empty feeling between meals; (4) vomitus containing blood clots; and (5) chronic bronchitis. *Duodenal ulcer.* (1) Nocturnal pain or discomfort; (2) periodic pain or discomfort; (3) pain or discomfort confined to the right upper abdominal quadrant; (4) copious vomitus; (5) vomitus resembling coffee grounds; and (6) tenderness confined to the right upper abdominal quadrant.

These findings were employed in an attempt to diagnose the cause of the hemorrhage in a further 100 cases at the time of their admission. The majority of the patients with duodenal ulcer gave a typical history whereby this lesion could be diagnosed with considerable assurance.

Arteriographic studies of the normal stomach showed that in both the seromuscular and the submucosal layers the arteries that are large enough to cause really severe haemorrhage are mostly confined to the upper two-thirds of the stomach. Those of the submucosa are further limited to a band on either side of the lesser curvature and the greater curvature with its adjoining walls. These circumscribed areas are therefore the only likely source of severe hemorrhage from a shallow ulcer, and, what is more, all the acute lesions of the present series that caused such hemorrhage lay within a few centimeters of the upper two-thirds of the lesser curvature —most of them being on the adjoining part of the posterior wall.—[From the author's summary.]

481. **Blood Ammonia Concentration and Bromsulfalein Retention in Upper Gastrointestinal Hemorrhage**
G. A. BELKIN and H. O. CONN. *New England Journal of Medicine* [*New Engl. J. Med.*] **260**, 530–534, March 12, 1959. 21 refs.

Blood ammonia and bromsulfalein determinations were performed in 96 patients after gastro-intestinal hemorrhage. The blood ammonia concentration was normal in 95% of the noncirrhotic patients. It was increased in 87% of cirrhotic patients who had not received antibiotic therapy. Bromsulfalein retention was elevated in 93% of the cirrhotic patients, but was also increased above 15% in a fourth of the noncirrhotic patients. The concurrence of elevated blood ammonia and bromsulfalein levels (higher than 150 μg. per 100 ml. and 15%, respectively) was practically diagnostic of cirrhosis. Conversely, the combination of normal blood ammonia and bromsulfalein determinations practically excluded this diagnosis. These tests were of no diagnostic value if either determination was elevated and the other normal. In cirrhotic patients the rise in blood ammonia was equally great whether the bleeding occurred from esophageal varices or from other sites in the gastrointestinal tract.—[Authors' summary.]

LIVER AND GALL-BLADDER

482. **Serum Vitamin B_{12} Content in Liver Disease**
T. D. STEVENSON and M. F. BEARD. *New England Journal of Medicine* [*New Engl. J. Med.*] **260**, 206–210, Jan. 29, 1959. 1 fig., 14 refs.

The increase in the serum vitamin-B_{12} (cyanocobalamin) content in acute and chronic liver disease has been variously attributed to enhanced absorption of the vitamin from the gastro-intestinal tract, to its release from the damaged liver, and to an increased binding capacity of the serum resulting from abnormalities in the serum proteins. In an attempt to elucidate the mechanism the authors have carried out investigations at the Louisville General Hospital, Kentucky, on 39 patients with cirrhosis, hepatitis, or obstructive jaundice, the diagnosis

being based on the usual clinical criteria and in some cases confirmed by biopsy or at necropsy. The vitamin-B_{12} content was determined both in serum and in urine by microbiological assay. The absorption of a test dose of 0·5 μc. of vitamin B_{12} labelled with radioactive cobalt was measured by determining the amounts excreted in the urine and faeces, while plasma clearance was determined by injecting 2 μc. of the radioactive vitamin and measuring the activity of plasma at intervals during the next 24 hours.

In most of 27 patients with cirrhosis and 7 with hepatitis the serum content of the vitamin was elevated above the normal level, the increase correlating reasonably well with the severity of the disease. Serial determinations showed that the concentration increased in progressive disease and decreased with recovery. The highest concentrations were seen in cases of hepatic coma and the lowest in those in which there was little active hepatocellular disease. The serum vitamin-B_{12} concentration was within normal limits in all of 5 patients with obstructive jaundice. In all 39 patients, however, the absorption, excretion, and plasma clearance of radioactive vitamin B_{12} were within the normal range. The administration of sodium folate had no effect on the serum concentration of the vitamin in patients with alcoholic cirrhosis, and the intravenous infusion of methionine was also without effect.

It is therefore concluded that the absorption of vitamin B_{12} and the binding capacity of the serum are unaffected by liver disease, and that the serum content of the vitamin is increased as a result of hepatocellular necrosis or other cellular disturbances which release it in excessive quantities into the circulation.

W. H. Horner Andrews

483. **Relation of Azotemia to Blood "Ammonium" in Patients with Hepatic Cirrhosis**

L. T. Webster and G. J. Gabuzda. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **103**, 15–22, Jan., 1959. 3 figs., 20 refs.

In a study undertaken to evaluate the relationship between azotaemia and hepatic coma the authors, working at Western Reserve University School of Medicine, Cleveland, Ohio, found that the blood ammonium levels and the difference between the cerebral arteriovenous ammonium concentrations were greater in 4 patients with both hepatic cirrhosis and azotaemia than in 27 patients with hepatic cirrhosis alone or 6 with azotaemia alone. In one patient with both cirrhosis of the liver and azotaemia the ammonium content of mixed gastric and duodenal aspirate was shown to be three times that of the highest value found in 6 of the patients with cirrhosis alone. This high level was reduced by the oral administration of neomycin.

These findings are thought to be consistent with the view that urea may enter the gastro-intestinal tract from the circulating blood and there be broken down by bacterial urease into ammonium and carbon dioxide, thus increasing the portal ammonium load.

[Nevertheless, it is difficult to believe that there are many urease-containing bacteria in the stomach.]

P. C. Reynell

484. **The Natural History of Esophageal Varices. A Study of 115 Cirrhotic Patients in Whom Varices Were Diagnosed Prior to Bleeding**

L. A. Baker, C. Smith, and G. Lieberman. *American Journal of Medicine* [*Amer. J. Med.*] **26**, 228–237, Feb., 1959. 1 fig., 30 refs.

The mortality in the first year due to haemorrhage from oesophageal varices associated with hepatic cirrhosis has been estimated to range from 50 to 80% and with the aim of reducing this alleged high mortality some authors have recently advocated the early performance of a portal shunt in these cases. In an effort to determine the possible value of such "prophylactic surgery" in the treatment of patients with cirrhosis and oesophageal varices before the latter have begun to bleed, the authors have followed up a series of 115 such patients seen at the Veterans Administration Hospital, Hines, Illinois, in none of whom had any surgical procedures designed to reduce portal hypertension been performed. Points of particular interest to the authors were to ascertain what percentage of patients suffered from variceal haemorrhage and the mortality resulting therefrom—in particular, that following the first haemorrhage, which might presumably be prevented by a "prophylactic" shunt operation.

In the follow-up period (1 to 6 years, average 3·3 years) 74 patients (64%) died, 20 of them from variceal haemorrhage, 31 of hepatic failure, and 23 of conditions unrelated to the hepatic disorder. The majority (46) of the deaths due to variceal haemorrhage or hepatic failure occurred within 2 years of the diagnosis being made, emphasizing the heavy early mortality from these two complications. However, only 33 patients in this series (28·6%) suffered from bleeding and the first haemorrhage was the cause of death in 11 (33·3%, or 14·8% of the total number of deaths). The majority of patients therefore had no bleeding and less than two-thirds of those who bled died from actual blood loss (20 out of 33). There seemed to be a relation between the frequency of bleeding and the presence of extensive varices, but small or moderate varices, as estimated at oesophagoscopy, bled with equal frequency. The mortality following the first haemorrhage was higher in patients with associated small or moderate varices than in those with extensive varices, suggesting that the severity of haemorrhage bears no relation to the size of the varices. Although only 2 of the 33 patients who bled were alive at the end of the follow-up period, 7 of the deaths in this group were due to hepatic failure unassociated with bleeding and 4 to causes unrelated to the cirrhosis.

The concept that all patients with oesophageal varices are destined to bleed was obviously not sustained in this series. At the most 11 patients could conceivably have been saved by the performance of prophylactic surgery in the whole series. But the mortality for portacaval anastomosis in experienced hands in an average series of cirrhotic patients may exceed 10%, while in addition there is no certainty that bleeding will thereby be prevented, and there is the further risk of neuropsychiatric and other complications following operation. The authors conclude therefore that surgical intervention as

a routine is not justified at present in these cases, although improvements in technique and after-care might make such procedures more rewarding in the future. At the same time they note that surgical operation cannot prevent death from hepatic failure, which was the more important cause of the high mortality in their series.

A. E. Read

485. **Intravenous Galactose Tolerance Test Using a Modified Technique**

E. M. COHN and H. J. TUMEN. *American Journal of Digestive Diseases* [*Amer. J. dig. Dis.*] **4**, 29–42, Jan., 1959. 19 refs.

This paper from the Graduate School of Medicine of the University of Pennsylvania, Philadelphia, describes an evaluation of the intravenous galactose tolerance test as a measure of liver function by comparison with a number of other liver function tests in control subjects and patients with various types of liver disease. The usual technique was modified in that a standard amount of galactose was injected, regardless of body weight. With the patient in a fasting state blood was first obtained for the estimation of the serum bilirubin and protein concentrations and alkaline-phosphatase activity and for the performance of turbidity and flocculation tests. Then 50 ml. of 50% galactose solution was injected intravenously over a period of 4 to 5 minutes followed by an injection of " bromsulphalein " (sulphobromophthalein; BSP). Blood samples were withdrawn at the end of 45, 60, and 75 minutes, the first sample being used for the BSP clearance test and galactose being estimated in all three. Absence of galactose in the third sample was taken as indicating a negative or normal result.

Galactose was present in the blood after 75 minutes in only 3 out of 60 control subjects of normal weight. Since normal values were obtained in the other tests in this group it appeared that false positive results in the galactose tolerance test might be anticipated in 5% of cases. The result was positive in 11 out of 22 patients whose weight was less than 110 lb. (50 kg.). In 10 of these, however, additional evidence of hepatic dysfunction was obtained, and on recovery galactose retention no longer occurred. All of 7 patients weighing more than 180 lb. (82 kg.) gave a negative response to the galactose test; in 5 of these a minor degree of hepatic dysfunction was indicated by the BSP clearance test. It is concluded that within the range 110 to 180 lb. body weight does not materially influence the galactose tolerance test, and even outside this wide range the test appears to be applicable. Out of 30 patients with acute hepatitis, 23 showed galactose retention; in one of these patients the result of the galactose test was the only abnormal biochemical finding, diagnosis being proved by biopsy. Of 31 patients with cirrhosis, the result was abnormal in 25. On the other hand a positive result was obtained in only one of 11 cases of chronic infective hepatitis and in none of 12 cases of obstructive jaundice. In general the galactose tolerance test appeared to be more sensitive than the flocculation tests.

The effect of giving galactose by different routes was also assessed. In 20 control subjects there was no difference between the findings after oral and intravenous administration, but in the presence of cirrhosis the test was about twice as sensitive when the intravenous route was employed.

W. H. Horner Andrews

486. **Analysis of Forty-two Shunt Procedures for Portal Hypertension**

C. E. SEDGWICK and H. A. HUME. *A.M.A. Archives of Surgery* [*A.M.A. Arch. Surg.*] **78**, 359–363, March, 1959. 7 refs.

A report is presented of 42 cases in which a vascular shunt was used at the Lahey Clinic, Boston, as a means of controlling haemorrhage from varices of the upper gastro-intestinal tract; 21% of the patients treated were suffering from biliary cirrhosis.

In 28 cases splenectomy was performed and splenorenal venous anastomosis carried out. (In one early case nephrectomy had to be performed in order to effect the anastomosis, but this should rarely prove necessary.) There was an immediate mortality of 14% and a total mortality at the time of the report of 47%. The morbidity rate was 76%. In 13 cases an end-to-side portacaval shunt was carried out, with an immediate mortality of 23% and a total mortality of 46%, the morbidity rate being 50%. Finally in one case a makeshift anastomosis was performed between the inferior mesenteric vein and the left renal vein, but the shunt later appeared not to be functioning.

Although the various shunting procedures constitute an effective method of controlling varical haemorrhage, the protection afforded is not absolute. There is, however, a definite relationship between the adequacy of the shunt and the frequency of subsequent haemorrhage. Varical bleeding occurred after operation in 12 cases, with death in 6. Of these 12 patients, the shunt was not satisfactory in 8 and the remaining 4 had progressive disease or other complicating factors. Of 15 cases in which the size of the varices was estimated before and after operation, they were smaller in 12, unchanged in 2, and larger in one—this patient having a proven thrombosis in his portacaval shunt—after treatment.

Changes in liver function after operation were difficult to assess. The plasma albumin concentration was unchanged in 50% of cases, increased in 25%, and diminished in 25%. The cephalin flocculation reaction and serum bilirubin concentration indicated improvement on the whole, while the sulphobromophthalein clearance test showed, in general, some deterioration. The presence of hepatic dysfunction appeared to increase the operative mortality and morbidity.

[This article contains material of definite value, but it is rather diffuse and somewhat lacking in detail. For example, the duration of follow-up is not clearly stated, and insufficient information is given about the morbidity.]

W. H. Horner Andrews

487. **The Role of the Kidney in Laennec's Cirrhosis of the Liver.** [Review Article]

S. PAPPER. *Medicine* [*Medicine (Baltimore)*] **37**, 299–316, Dec., 1958. Bibliography.

Cardiovascular System

488. **Deliberate Circulatory Arrest. The Use of Halothane and Heparin for Direct-vision Intracardiac Surgery**
R. H. ORTON and K. N. MORRIS. *Thorax* [*Thorax*] **14**, 39–47, March, 1959. 18 refs.

The authors recall that two conditions are prerequisite for the survival of cerebral tissue during prolonged circulatory arrest, namely, the metabolism of the tissues must be lowered and intravascular clotting of the blood must be prevented. Hypothermia lowers metabolism, but it increases myocardial irritability as the temperature falls below 30° C. The anaesthetic agent halothane reduces carbon dioxide production and also lowers tissue oxygen needs, while morphine further depresses metabolism and heparin prevents blood clotting.

They then describe 14 direct-vision intracardiac operations based on these principles which were performed at the Alfred Hospital, Melbourne. The technique requires preparation with morphine, a dose of 0·25 mg. per kg. body weight being injected one hour before operation, but no atropine or hyoscine is given. Anaesthesia is induced with intravenous thiopentone (laryngeal intubation being performed under succinylcholine) and is maintained with oxygen and nitrous oxide in a ratio of 1:3. Simultaneous recordings of the electroencephalogram (EEG) and electrocardiogram are made, while catheterization of the femoral artery permits monitoring of the blood pressure. After thoracotomy has been performed and the essential pressure gradients recorded, 2 mg. of heparin per kg. body weight is injected intravenously. Then by means of a vaporizer halothane in a concentration of up to 5% is introduced into the closed circuit, a total gas flow of 3 to 4 litres being required. When the systolic blood pressure has fallen to 50 mm. Hg and the EEG reveals minimal cerebral activity caval occlusion is effected and the intracardiac procedures are performed. During this period the lungs are ventilated with the gas–oxygen mixture alone to wash out the high halothane concentration. Details of the operative procedure are given. The 10 male and 4 female patients, who ranged in age from 2 to 56 years, included 6 with aortic stenosis, 6 with pulmonary stenosis, and 2 with atrial septal defect. All survived operation well except a boy aged 2 who died suddenly 18 hours after operation. This death was not related to the anaesthesia, necropsy showing that death was probably due to the closure of an atrial septal defect in the presence of an incompletely relieved pulmonary stenosis and a very small, undeveloped right ventricle.

C. A. Jackson

489. **The Relationship between Heart Disease and Gallbladder Disease.** [Review Article]
A. G. HAMPTON, J. R. BECKWITH, and J. E. WOOD. *Annals of Internal Medicine* [*Ann. intern. Med.*] **50**, 1135–1148, May, 1959. 2 figs., bibliography.

490. **Use of Intravascular Carbon Dioxide Gas to Demonstrate Interatrial Septal Defects**
W. WINTERS, M. WILSON, D. CHUNGCHAROEN, H. M. STAUFFER, T. M. DURANT, and M. J. OPPENHEIMER. *American Journal of Physiology* [*Amer. J. Physiol.*] **195**, 579–585, Dec., 1958. 6 figs., 18 refs.

It has previously been demonstrated in normal dogs that carbon dioxide injected into a systemic vein or the right atrium allows radiological visualization of the right heart, but that the gas does not pass through the pulmonary circulation to the left side. At Temple University School of Medicine, Philadelphia, this fact has been applied to the detection of atrial septal defects, and the authors describe 79 experiments performed on 29 anaesthetized dogs in some of which an artificial interatrial defect had been created. Carbon dioxide was injected in amounts varying from 3 to 12 ml. per kg. body weight, and its passage through the heart studied by fluoroscopy with image intensification, supplemented by cinematography for later slow-motion reproduction. At the same time intracardiac pressure changes, respiratory movements, and the electrocardiogram were recorded. Angiocardiography, as well as determination of the oxygen saturation of blood samples and plotting of dye dilution curves, were used to confirm the presence of an interatrial shunt and to determine its direction.

The injection of carbon dioxide proved to be a safe and satisfactory method of demonstrating septal defects. Three signs were consistently observed: (1) a brief passage of the gas through the left atrium, (2) the appearance of a residual bubble in the left ventricle for 10 to 15 seconds, and (3) a moderate increase in systemic arterial pressure. In animals in which the atrial septum was intact no gas was seen in the left heart and arterial pressure was invariably lowered as a result of temporary pulmonary capillary obstruction. The three signs were independent of the direction of the interatrial shunt, probably because of the sharp rise in right atrial pressure caused by the injection (about 100 mm. Hg, compared with less than 20 mm. Hg in the left atrium). The smaller quantities of gas gave satisfactory visualization with the image intensifier. During the experiments various positions were tried, but none proved to have any advantage over the supine. Injections given directly into the heart were easier to interpret than those into a peripheral vein.

S. G. Owen

491. **The Role of the Left Ventricle in the Surgical Management of Aortic Stenosis**
R. P. GLOVER and H. L. GADBOYS. *Angiology* [*Angiology*] **10**, 1–10, Feb., 1959. 6 figs., 17 refs.

The major factor governing the treatment of aortic valvular stenosis is the state of the left ventricle. The results of surgical treatment of this lesion are at present less satisfactory than those obtained in the case of the other cardiac valves. Pathologically, there is early fusion

of the cusps and heavy calcification, perhaps because of the vascular trauma from the strong ventricular contractions. Complete fixation and immobility soon supervene and thus operation should be carried out before this occurs. With the jet-like ejection the systolic blood pressure may not reach high levels, but the diastolic pressure is raised, so that filling of the coronary arteries may be inadequate, though the demand is raised. Left ventricular hypertrophy and a rise of intraventricular pressure up to 400 mm. Hg, follow. When the critical valve area is reached—approximately 0·7 sq. cm.—adequate output can no longer be maintained, heart failure follows, and death occurs within a few months.

The following five clinical stages of aortic stenosis are recognized: (I) the typical murmur, with no symptoms; (II) early symptoms, such as palpitations and fatigue; (III) inadequate output, with dizziness and angina; (IV) left ventricular failure and pulmonary congestion; (V) right ventricular failure, accompanied by oedema and ascites. Ideally, operation should be performed during Stage II and not later than Stage III. In the later stages sudden death often occurs naturally, and surgery carries a high mortality. Three surgical approaches have proved practicable: (1) transaortic, (2) by the open heart method under direct vision, and (3) transventricular. The first two permit palpation and visualization of the valve, but the disorganization caused is usually such that functional restoration is impossible, so in practice visualization carries little advantage. If effective replacement by a suitable permanent prosthesis ever becomes feasible, open heart surgery will perhaps be the method of choice. Meanwhile, except perhaps for some congenital cases, the authors advise transventricular dilatation, by which method acceptable results are obtained with a notably lower risk. They point out that the criteria for operation which hold for mitral stenosis should not be applied to aortic stenosis. The stenosed mitral valve protects the left ventricle, which remains a strong and effective chamber, and operation can often be successfully carried out after several attacks of congestive failure. In aortic stenosis, however, the brunt falls on the left ventricle from the first, and operation should be performed before decompensation develops. [In addition, the mitral valve is less often calcified and the coronary arterial flow is adequate.]

The authors then report from the Presbyterian Hospital, Philadelphia, a consecutive series of 78 operations for aortic commissurotomy performed during the period 1951–7. In 37 cases a large three-bladed dilator was used, but in the last 41 a more refined and quicker technique was adopted, employing Brock's smaller two-bladed dilator, which was expanded in several directions. In this series an average pressure gradient of 78 mm. Hg fell to an average of 27 mm. Hg. There were 19 operative deaths, mostly due to cardiac arrest, but only 2 of these occurred among the last 41 cases treated. There were 15 late deaths, mostly from congestive heart failure. Of the 12 patients still alive out of the original 37 earlier cases, all are improved; of the later 41 cases, 33 have been followed up for over one year and of these 22 are improved, 19 being at work, and none has aortic insufficiency. *M. Meredith Brown*

492. **Long-term Anticoagulant Therapy in Coronary Disease**

R. E. Ensor and H. R. Peters. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **169**, 914–918, Feb. 28, 1959. 13 refs.

In this study, reported from the University of Maryland School of Medicine, Baltimore, the authors have compared the results of continuous long-term anticoagulant therapy (up to 15 years) in three groups of patients with myocardial infarction (268 cases), acute coronary insufficiency (55), or angina pectoris (23), with those in 175 " pseudocontrols ", that is, patients who had discontinued such treatment after 3 months to 10 years. In the latter the mortality was highest in the first 2 years after discontinuing the treatment. Among the 268 patients continuously treated for infarction the over-all mortality was 23·1%, while recurrences with survival occurred in 3·7%. The mortalities at the 5- and 10-year points were 21 and 25% respectively, as compared with 29 and 36% respectively in the 140 pseudocontrols. Similar advantages from continuous therapy were demonstrated in the smaller series treated for angina and coronary insufficiency. On analysis of recent reports in the literature in respect of patients entirely untreated with anticoagulants (" true controls ") the 5- and 10-year mortality was 44 and 68% respectively. In the whole of the authors' series there were 58 minor haemorrhagic episodes, and in no case did death from haemorrhage occur. In spite of these favourable results the authors stress that because of the variable course of coronary arterial disease, including environmental and emotional factors, statistics in this condition are difficult to interpret and any conclusions must be drawn with the greatest caution and objectivity. *J. N. Agate*

493. **Controlled Studies on the Efficacy of Bilateral Internal Mammary Artery Ligation in Patients with Angina Pectoris**

R. E. Fremont, R. Klopstock, and P. Glass. *Angiology* [*Angiology*] **10**, 20–27, Feb., 1959. 3 figs., 12 refs.

The fact that there is communication between the internal mammary artery and the coronary arteries is now well established. Following reports from Italy that ligation of both internal mammary arteries in the second intercostal spaces relieves the symptoms of angina pectoris the authors have performed this operation at Brooklyn Veterans Administration Hospital, New York, believing it to be a " simple, riskless procedure ".

They point out that the reliable assessment of coronary insufficiency is difficult and must usually be based on subjective tests, while any alteration in symptoms must be interpreted with great caution. In this study an exercising apparatus with rubber-band resistance was used, and during the test serial 4-lead electrocardiography and ballistocardiography were performed. Of the 12 patients studied, 4 underwent a sham operation (in 3 of these ligation was performed later). Of the 8 on whom ligation was carried out, 2 died, one of extensive myocardial infarction 4 hours after operation and the other 11 days later; the remaining 6 had prompt relief of symptoms lasting for one week to 4 months, but no

objective improvement. One patient reported relief from the sham operation and again after ligation, which however lasted 10 days only. Only one patient showed objective improvement after ligation. The authors remark that the promptness of the subjective improvement after operation suggests the dominant role played by psychological factors in such cases. They conclude that these studies have demonstrated the need for strict criteria for the selection of patients and evaluation of results. There may be a place for this operation in moderate cases of angina, preferably before infarction has occurred. *M. Meredith Brown*

494. **Complete Atrioventricular Block Treated with Isoproterenol Hydrochloride**
D. CHANDLER and M. I. CLAPPER. *American Journal of Cardiology* [*Amer. J. Cardiol.*] **3**, 336–342, March, 1959. 4 figs., 15 refs.

From Wayne State University College of Medicine, Detroit, the authors report the effects of the sublingual administration of isoproterenol (isoprenaline) hydrochloride, a sympathomimetic drug capable of increasing the heart rate, to 13 patients with complete heart block, of whom 5 had attacks of the Adams–Stokes syndrome. The drug was found to be markedly effective in preventing the latter in doses of 10 to 20 mg. every 2 or 3 hours. In 7 of the patients there was a significant increase in cardiac rate. The authors also showed that isoprenaline by subcutaneous administration was five times as effective as an equal dose of adrenaline. The drug possesses a wide margin of safety. *R. Wyburn-Mason*

495. **Digitalis and Atrial Tachycardia with Block. A Year's Experience**
B. LOWN, F. MARCUS, and H. D. LEVINE. *New England Journal of Medicine* [*New Engl. J. Med.*] **260**, 301–309, Feb. 12, 1959. 5 figs., 11 refs.

In an attempt to assess the importance of digitalis in the causation of paroxysmal atrial tachycardia with atrio-ventricular block the authors have examined the circumstances prevailing in 32 such episodes recognized among 8,096 electrocardiograms recorded at the Peter Bent Brigham Hospital, Boston, during 1957. Most of the 23 patients in whom these episodes occurred were in advanced cardiac decompensation. The chief electrocardiographic features were: (1) an ectopic atrial rate averaging 176 (range 138 to 250) per minute; (2) deformed, often diminutive, P waves; and (3) some degree of atrio-ventricular block, usually partial, which was either spontaneous or induced by vagal stimulation. In 24 (75%) of these episodes digitalis poisoning was considered to be the responsible cause, either because there were other signs of overdosage with this drug or because the onset was related to an event likely to increase the degree of digitalization, such as increase in the maintenance dosage, substantial diuresis, or the development of potassium depletion.

The conclusion is drawn that cases of atrial arrhythmia due to digitalis are occurring with increasing frequency. As the authors point out, their recognition is important because digitalis is usually recommended for the treatment of supraventricular tachycardia. The common pattern is atrial tachycardia with block, and the most helpful point in differential diagnosis is the observed response to administration of potassium; in the authors' experience atrial flutter and atrial tachycardia not caused by digitalis are unaffected by potassium. In their view the correct treatment in these circumstances is withdrawal of digitalis followed if necessary by judicious employment of potassium and procainamide, either singly or in combination. *S. G. Owen*

SYSTEMIC CIRCULATORY DISORDERS

496. **Coagulation Defects in Liver Disease and Response to Transfusion during Surgery**
R. B. FINKBINER, J. J. MCGOVERN, R. GOLDSTEIN, and J. P. BUNKER. *American Journal of Medicine* [*Amer. J. Med.*] **26**, 199–213, Feb., 1959. 10 figs., 30 refs.

This paper from Massachusetts General Hospital (Harvard Medical School), Boston, describes the results of laboratory assays of the components of coagulation in 25 patients with hepatic disease, 21 with parenchymal disease, one with obstructive jaundice, and 3 with extrahepatic portal hypertension. The assay methods used were the accepted standard techniques.

The haemostatic defect in parenchymal liver disease was found to be multiple, and the degree of impairment of the defect was roughly parallel with the biochemical evidence of liver damage, as judged by the results of flocculation tests. The levels of prothrombin, Factor VII, and the Christmas factor were frequently found to be depressed, and Factor V was also often present in subnormal concentration, whereas the antihaemophilic globulin concentration was usually normal. [This rather surprising finding has been reported by others.] Thrombocytopenia was a common feature, but fibrinogenopenia was unusual. Fibrinolytic activity was increased in only 5 (20%) of the patients, but the technique employed was relatively insensitive, being dependent on the lysis of whole blood clot. In the one case of obstructive jaundice studied there was depression only of the adsorbed plasma components prothrombin, Factor VII, and Christmas factor. In the 3 cases of extrahepatic portal hypertension the findings were normal, except that in one there was thrombocytopenia.

The one-stage test of Quick for prothrombin time was found to be a useful non-specific screening test for abnormality of the coagulation mechanism, except that it did not reflect the platelet count. It was noted that depression of the platelet count did not parallel the depression of other clotting factors. Partial correction of the defect could be obtained for 24 to 48 hours by blood transfusion. Fresh blood was shown to be superior to stored blood by virtue of the lability of Factor V in stored blood and the viability of the platelets in fresh blood. Such bleeding as occurred during surgery was not found to be uncontrollable.

[This paper presents a valuable survey of the haemostatic mechanism in parenchymal liver disease.]

A. S. Douglas

497. **Chlorothiazide as an Adjunct in the Treatment of Essential Hypertension**

M. Moser and A. I. Macaulay. *American Journal of Cardiology* [*Amer. J. Cardiol.*] 3, 214–219, Feb., 1959. 2 figs., 6 refs.

The effect of chlorothiazide in combination with various antihypertensive drugs was studied in 91 hypertensive patients attending the Grasslands Hospital, Valhalla, New York. Chlorothiazide was given in a daily dosage of 0·5 to 1·5 g. for an average of 7 months, no added salt being allowed in the diet.

In 39 patients hitherto treated with a rauwolfia preparation alone (reserpine or "raudixin") the addition of chlorothiazide produced a further fall in blood pressure of 14 to 18 mm. Hg from a pre-chlorothiazide average level of 184/112 mm. Hg. Less effect was observed in 17 patients previously receiving both reserpine and hydrallazine (8 to 14 mm. from a control average of 170/102 mm. Hg). The greatest reduction was obtained in a third group of 35 patients who were being treated with a ganglion-blocking agent (either mecamylamine or trimethidinium methosulphate) in addition to reserpine and hydrallazine; here the average reading fell by 12 to 16 (from 174/101) mm. Hg, and the dose of ganglion-blocking agent had in many cases to be reduced in order to avoid inducing hypotension. Side-effects were few. Diuresis and loss of weight did not continue beyond the first 3 days, and the plasma electrolyte concentrations showed little change except in 2 patients with renal failure, who became depleted of potassium. Nausea and a bitter taste were experienced by 6 patients, and 3 developed rashes while taking the drug.

It is suggested that chlorothiazide used in this way may be of value in allowing decreased dosage of more potent antihypertensive agents. In the authors' experience potassium supplements are usually unnecessary unless the diet is poor or digitalis is also being given.

S. G. Owen

498. **The Use of Carbethoxysyringoyl Methylreserpate in Hypertension**

B. Barbour, G. Irwin, H. Yamahiro, W. Frasher, and R. F. Maronde. *American Journal of Cardiology* [*Amer. J. Cardiol.*] 3, 220–228, Feb., 1959. 15 figs.

At Los Angeles County Hospital a clinical trial of carbethoxysyringoyl methylreserpate—a reserpine derivative previously shown to lower blood pressure in normal and hypertensive dogs—was carried out on 30 patients with long-established and relatively stable hypertension. In 16 of these who were given 1 to 20 mg. of the drug daily by mouth for periods ranging from 6 to 28 weeks the blood pressure in the supine position fell by an average of 13·5 mm. Hg from the control average level of 197/117 mm. Hg. The decrease in blood pressure in the standing position was only slightly greater (14 to 20 mm. Hg).

A further 10 patients had previously been treated with reserpine, thus allowing a comparison between the two drugs. It was found that carbethoxysyringoyl methylreserpate in an average daily dose of 5 mg. had rather less effect than 0·5 mg. of reserpine, the mean blood-pressure readings during administration of the 2 drugs being 163/94 and 154/90 mm. Hg respectively.

Observations on other patients after intravenous and intramuscular injection showed that, weight for weight, the drug was more effective when given parenterally than when given by mouth. Again, however, it was less so than reserpine. Side-effects included nausea, lethargy, nasal congestion, dryness of the mouth, and local pain at the site of intramuscular injection. With oral administration these effects were of minor degree only and in no instance necessitated discontinuance of therapy.

It is concluded that carbethoxysyringoyl methylreserpate, like reserpine, is unlikely to be of much value as a sole antihypertensive agent, although it may find application as a substitute for reserpine in patients unable to tolerate the latter drug.

S. G. Owen

499. **Therapy of Hypertension with Orally Given Syrosingopine**

G. R. Herrmann, E. B. Vogelpohl, M. R. Hejtmancik, and J. C. Wright. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **169**, 1609–1612, April 4, 1959. 5 refs.

Syrosingopine (carbethoxysyringoyl methylreserpate, "singoserp"), is a synthetic compound derived from reserpine. In a clinical trial at the University of Texas Medical Branch, Galveston, it was given by mouth to 77 ambulant patients with essential hypertension who were divided into three groups as follows: (1) 38 patients who had had no previous treatment; (2) 34 patients who had been treated with reserpine for one to 12 months, syrosingopine in varying doses being substituted for purposes of comparison; and (3) 5 patients with severe hypertension who had been under treatment with a combination of hypotensive drugs which could no longer be continued in effective dosage because of severe intolerance to rauwolfia products.

In Group 1 the dose of syrosingopine was generally 0·25 mg. four times a day initially, this being increased in some cases at fortnightly intervals to a maximum of 1 mg. four times a day. In this group the average blood pressure decreased from 199·1/116·5 to 176·1/104 mm. Hg. A significant clinical response was seen in 16 patients (42%). In individual patients there was no correlation between the size of the dose and the decrease in blood pressure. In Group 2 substitution of syrosingopine for reserpine gave very variable results in individual cases, but in general the reduction in blood pressure obtainable with the two drugs was similar. The dose of syrosingopine required was higher than that of reserpine, but the drug was generally well tolerated in all the dosages tested, and 6 out of 9 patients who had suffered severe side-effects with reserpine lost them entirely on substitution of syrosingopine. In the 5 patients of Group 3 the substitution of 3 mg. of syrosingopine for the previous rauwolfia product enabled a substantial reduction in blood pressure to be maintained without any significant side-effects. The main advantage of syrosingopine over reserpine seems to lie in its relative freedom from side-effects.

A. Schott

Clinical Haematology

500. **Clinical and Morphological Aspects of Waldenström's Macroglobulinaemia** (Aspects cliniques et morphologiques de la macroglobulinémie de Waldenström) L. R. WASSERMAN, G. GELIN, S. LEE, G. WEISSMAN, S. GINSBERG, and F. G. ZAK. *Sang* [*Sang*] **29**, 633–665, 1958 [received Feb., 1959]. 7 figs., bibliography.

The authors present 10 hitherto unpublished cases of Waldenström's macroglobulinaemia studied at the Mount Sinai Hospital, New York. In 9 of these cases the diagnosis was proved by ultracentrifugal analysis and in 3 cases histological studies were possible. From a review of 114 cases reported in the literature and from their personal experience they conclude that macroglobulinaemia is a lymphoid reticulosis related to multiple myeloma and chronic lymphatic leukaemia, and possibly to other malignant tumours—one of their own patients had an occult carcinoma of the stomach.

Clinically, the condition occurs most commonly in elderly patients. There may be frequent haemorrhages, with a low erythrocyte count and occasionally low leucocyte and platelet counts in the peripheral blood. The erythrocyte sedimentation rate is very high. Electrophoresis of the serum proteins (on starch gel, as the Waldenström macroglobulin will not migrate on paper) shows an abnormal globulin peak, while ultracentrifugal analysis demonstrates the presence of a macroglobulin with a molecular weight in the region of one million. Histologically, the principal change is a diffuse invasion of all tissues, but especially the bone marrow, lymph nodes, spleen, liver, and kidneys, by lymphoid or reticuloendothelial cells. The origin and significance of these cells are not clear.

The prognosis is variable; a malignant type of the disease which may end in death within 2 years and a relatively benign type progressing for up to 15 years have been described. There is no specific treatment, though blood transfusion is of value after each haemorrhagic episode and in the case of chronic anaemia. Steroids are of value only in those cases with a severe haemolytic element. Splenectomy might be indicated in the unusual case with an enormous spleen or severe thrombocytopenia. *Victor M. Rosenoer*

501. **A Review of Fifty-one Cases of Multiple Myeloma. Emphasis on Pneumonia and Other Infections as Complications**
H. GLENCHUR, H. H. ZINNEMAN, and W. H. HALL. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **103**, 173–183, Feb., 1959. 2 figs., 18 refs.

In this paper from the University of Minnesota the authors review 51 consecutive cases of multiple myeloma encountered at the Veterans Administration Hospital, Minneapolis, between 1947 and 1957. In each case the diagnosis was confirmed by marrow biopsy, tumour biopsy, or necropsy and by electrophoresis of the serum proteins. Of the 42 patients who died, 28 came to necropsy; only 8 survivors are known, one patient having been lost to follow-up. The patients ranged in age from 26 to 73 years, 80% being between 50 and 70, and owing to the type and location of the hospital all were Caucasian males. The onset, clinical findings, and course of the illness were in agreement with the findings in previously reported series. Of special interest were 18 patients with myelomatous kidneys, 5 who presented with paraplegia, and 2 with features of rheumatoid arthritis, one of whom was shown by synovial biopsy to have amyloidosis.

In 28 cases one or more episodes of pneumonia, exclusive of terminal pneumonia, occurred, the average incidence being 2·7 bouts per patient; only in one of these cases was the electrophoretic pattern of the serum proteins normal. Terminal pneumonia occurred in 17 cases and bacteriaemia in 7. In addition 29 patients had other infections, predominantly of the urinary tract. The authors suggest that the high incidence of recurrent pneumonia in these cases reflects an inability to produce protective antibodies such as occurs in agammaglobulinaemia. In multiple myeloma, again as in agammaglobulinaemia, the delayed type of bacterial hypersensitivity is not altered. It is stressed that repeated bacterial infections, especially pneumococcal pneumonia, are important and often early complications of multiple myeloma; antibiotics are effective unless their use is delayed.
Victor M. Rosenoer

ANAEMIA

502. **Treatment of Pernicious Anemia by Oral Administration of Vitamin B_{12} without Added Intrinsic Factor**
E. A. BRODY, S. ESTREN, and L. R. WASSERMAN. *New England Journal of Medicine* [*New Engl. J. Med.*] **260**, 361–367, Feb. 19, 1959. 1 fig., 35 refs.

The authors report from the Mount Sinai Hospital, New York, the results of the oral administration of 150 μg. daily of vitamin B_{12} (cyanocobalamin) without added intrinsic factor to 17 patients with megaloblastic anaemia, of whom 14 had pernicious anaemia, 2 had undergone total gastrectomy, and one suffered from the malabsorptive syndrome. Treatment was continued for 2 to 34 months.

Complete haematological remission was obtained in 11 of the patients with pernicious anaemia, in one of the gastrectomized patients, and in the patient with the malabsorptive syndrome; in the remaining 4 patients the response, although incomplete, was judged to be excellent. Remission was maintained for varying periods of 2 to 31 months and no patient relapsed after haematological values returned to normal. Mild neurological complications which had been present were completely

or partially relieved by oral therapy in 5 cases, but were unaffected in one other patient, who, however, responded completely to vitamin B_{12} given by intramuscular injection. During therapy the serum vitamin-B_{12} level rose in each patient, the rise being due to an increase in the bound form of the vitamin, the free form remaining at pre-treatment levels. Despite this rise normal serum values were reached in only 3 of the cases of pernicious anaemia and in the 2 gastrectomy cases; in the others the serum levels were less than 200 $\mu\mu$g. per ml. Nevertheless, in 2 patients who showed persistently low serum levels of vitamin B_{12} there was complete haematological remission.

The authors conclude that their results are in accord with the concept that the absorption of part of large doses of vitamin B_{12} does not depend on the presence of intrinsic factor. *D. G. Adamson*

503. **Studies on Congenital Hemolytic Syndromes. II. Rates of Destruction and Production of Erythrocytes in Hereditary Spherocytosis**
M. E. Erlandson, I. Schulman, and C. H. Smith. *Pediatrics* [*Pediatrics*] **23**, 462–475, March, 1959. 3 figs., bibliography.

The authors report from New York Hospital–Cornell Medical Center the results of detailed studies of 4 adults with well marked clinical and laboratory evidence of congenital haemolytic anaemia and of 6 children in whom the clinical manifestations were minimal. All the patients were in a state of haematopoietic equilibrium. In addition to estimation of the haemoglobin value, haematocrit, and reticulocyte count, erythrocyte survival times were estimated by a radioactive-chromium technique and blood and erythrocyte volumes determined. The " compensation index ", that is, the rate of production of erythrocytes divided by the rate of destruction of erythrocytes, was established for each patient.

The haemoglobin values ranged from 10·5 to 13·7 g. per 100 ml. and the haematocrit from 28·4 to 36·8%. The total erythrocyte volume was invariably low, ranging from 18·5 to 24·3 ml. per kg. body weight (normal value 29·2 ml. per kg.). The mean life span of the erythrocytes ranged from 13·8 to 28·6 days (normal 120 days), except in one patient in whom it reached 48 days. Thus although in some of these patients the anaemia was apparently mild or even absent, in terms of the volume of erythrocytes destroyed it was well marked and the erythrocyte survival studies revealed brisk haemolysis. Such patients, hitherto regarded as examples of latent or well-compensated haemolytic anaemia, are potentially liable to develop gall-stones and aplastic crises and will require splenectomy at a suitable time. The reason for the discrepancy between the relatively high haemoglobin and haematocrit levels on the one hand and the low erythrocyte volumes on the other lies in the lack of a compensatory expansion of plasma volume. In 4 patients in whom the rate of destruction of erythrocytes was less than 6 times the normal the erythrocyte volume and the compensation index were abnormally low. The rate of production of erythrocytes was less than 6 times the normal in most of the patients, that is, lower than the previously accepted erythropoietic compensatory capacity. It appears, therefore, that in such patients there is an unidentified factor interfering with erythropoiesis.

No evidence of a familial pattern of the haemolytic defect was found in members of the 4 family groups to which these patients belonged, nor was the haemolytic defect a function of age. The authors recommend that in children with minimal symptoms splenectomy should be deferred until late childhood in view of the hazard of severe infections, but should be carried out before the age of 10 so as to avoid the development of gall-stones.

[The original paper should be consulted for details of the mathematical formulae used in the calculations.]
J. L. Markson

504. **Studies in Sickle-cell Anemia XII. Further Studies on Hepatic Function in Sickle-cell Anemia**
A. D. Ferguson and R. B. Scott. *A.M.A. Journal of Diseases of Children* [*A.M.A. J. Dis. Child.*] **97**, 418–425, April, 1959. 4 figs., 18 refs.

Despite a good deal of clinical evidence of liver involvement in children with sickle-cell anaemia difficulty is frequently encountered in determining the degree of hepatic dysfunction by the usual laboratory tests. In an endeavour to obtain additional evidence of disturbance of liver metabolism in this disorder the authors, in this study reported from Howard University College of Medicine, Washington, D.C., have employed some of the newer laboratory procedures as well as the commonly used liver function tests in the examination of 21 children aged 2 to 13 years with sickle-cell anaemia admitted to hospital on 49 occasions. A clinically palpable liver was found in 13 patients (51% of the admissions) while 15 (43% of admissions) showed clinical icterus.

In the usual liver function tests the serum bilirubin value, particularly that of the indirect reacting portion, showed an increase in some of the patients, while others exhibited hypoalbuminaemia, hyperglobulinaemia, and a positive cephalin–cholesterol flocculation reaction. Among the newer tests electrophoresis of the serum proteins showed an elevation in the γ-globulin fraction in 50% of cases, while an abnormal pattern in the β-globulin fraction was observed in 64%. Blood ammonia levels tended to be slightly elevated, although within the normal range, whether examined during a quiescent period or during a crisis. Urinary amino-acid analyses were performed on 5 children; no abnormal or unusual amino-acids were found, but threonine, asparagine, leucine, and arginine were not identified, though they are usually present in normal children. Liver biopsy examination in one case in sickle-cell crisis showed that the sinusoids were dilated and plugged with sickle cells, while the liver cord cells showed signs of early degenerative changes.

The authors conclude from the findings that although helpful in some cases in supplying additional confirmatory evidence of hepatic damage in sickle-cell anaemia, the new procedures employed in this study were not conclusively diagnostic. *A. Ackroyd*

Respiratory System

505. **The Cause of Digital Clubbing. Testing a New Hypothesis**
G. H. HALL. *Lancet* [*Lancet*] **1**, 750–753, April 11, 1959. 1 fig., 35 refs.

After a brief discussion of the two main hypotheses hitherto advanced as an explanation of digital clubbing, both of which appear to him to be unsatisfactory, the author describes, from University College Hospital, London, an investigation of the effect of rutin on the clearance of subcutaneously injected radioactive sodium from the fingers of 8 normal subjects and 8 patients with digital clubbing, which was undertaken to test a third hypothesis. The rate of clearance in the fingers of the healthy subjects did not change after the administration of rutin, whereas in clubbed fingers there was a notable increase in this rate, which before the administration of rutin had been considerably lower than in normal persons and afterwards was higher. In some clubbed fingers rutin produced the appearance of capillary pulsation under the nails.

The author suggests that these experimental findings support his theory that in certain cases of pulmonary and cyanotic congenital heart disease mixed venous blood, containing a substance normally removed by oxidation in the lungs, is shunted past normal lung tissue and this substance, passing into the systemic circulation, inhibits the vasoconstricting action of circulating adrenaline on the musculature of the smaller arterioles and causes clubbing. He further suggests that this substance is reduced by ferritin, a compound specifically antagonized by the flavonoid rutin, so that the latter can be used to help in the restoration of normal capillary blood flow in the fingers.

A. Gordon Beckett

506. **Pulmonary Arteriovenous Fistulae**
B. T. LE ROUX. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **28**, 1–19, Jan., 1959. 14 figs., bibliography.

The classic features of pulmonary arteriovenous fistula are cyanosis, clubbing of the fingers, polycythaemia, dyspnoea, and an extracardiac murmur which is augmented by deep inspiration and by the Müller manœuvre and diminished by the Valsalva manœuvre. The patient may complain of headache, dizziness, or paraesthesiae, and there may be episodes of paresis and convulsions. The heart size is usually normal. A family history of hereditary haemorrhagic telangiectasis is obtained in about 15% of cases. The condition may be diagnosed at any age. Multiple and bilateral fistulae may be present. The typical radiographic finding is a rounded or lobulated homogeneous opacity with fairly well defined margins bound to the hilum by extensions due to the dilated subserving vessels. On screening, the shadow may be seen to pulsate and may alter in size with the Valsalva and Müller manœuvres. Angiocardiography demonstrates the fistula and its vascular connexions more clearly. The proportion of blood shunted through the fistula varies within wide limits and may approach 90%. The only treatment available is surgical, the resection being as limited as possible. If the fistulae are multiple no treatment may be possible.

The author of this paper from the Departments of Surgery, University of Edinburgh, reports 6 cases of pulmonary arteriovenous fistula in 3 males and 3 females between the ages of 29 and 57. The clinical findings are summarized thus: dyspnoea in 5 cases, cyanosis in 4, finger clubbing in 5, murmur in 5, mitral stenosis in 3, x-ray opacity in 6, other telangiectases in 3, and a family history of telangiectasis in 3. Multiple fistulae were present in 4 patients, in whom they numbered 2, 3, 3, and 5 respectively. The packed cell volume varied from 39 to 58% and the arterial oxygen saturation from 86 to 96%. The cardiac output was increased. Angiocardiography demonstrated considerable widening of the arteries and veins connected with the fistulae, the vein in one case being 3 cm. in diameter. Surgical treatment was successfully undertaken in 2 patients, both of whom had multiple bilateral fistulae and mitral stenosis. In one case the operation was performed in two stages, mitral valvotomy and resection of a fistula in the left lung being carried out first and resection of one large and 3 small fistulae from the right lung being performed after an interval of 4 months. The patient was greatly improved, but 5 months after the second operation rapidly increasing dyspnoea and signs of gross pulmonary hypertension developed and she died a month later. In the second case mitral valvotomy and bilateral resection of fistulae were performed at a single operation, with complete relief of symptoms up to the time of the report.

Bernard J. Freedman

507. **The Use of Elastase in the Treatment of Chronic Suppurative Pulmonary Diseases.** [In English]
K. KOVÁCS and D. BAGDY. *Acta medica Academiae Scientiarum Hungaricae* [*Acta med. Acad. Sci. hung.*] **12**, 168–176, 1958 [received April, 1959]. 7 figs., 25 refs.

This paper from the 4th District Hospital, Budapest, is concerned with the treatment of chronic suppurative pulmonary conditions with enzymes capable of liquefying pus. After referring to the intrabronchial administration of streptokinase, streptodornase, and trypsin and the use of trypsin sprays and aerosols the authors describe their experience with elastase, which is prepared from the pancreas and breaks down elastin, the special protein of elastic fibres. The feeding of elastase to rabbits has been shown to prevent the development of cholesterol atherosclerosis and of fatty degeneration of the liver. In normal young men and adults the elastase content of the pancreas varies within a well defined range, whereas in individuals with arteriosclerosis it is very low.

The preparation of elastase used was obtained from dry pancreas powder by a simple adsorption method and had an activity of 33 elastase units per mg. (an elastase unit being defined as the quantity of enzyme capable of dissolving 1 mg. of elastin in 30 minutes under standard conditions). When this preparation was administered through a bronchoscope to rabbits under ethyl chloride anaesthesia in doses up to 500 mg. dissolved in 5 ml. of M/15 disodium phosphate solution no toxic effects were observed.

A series of 8 patients with pulmonary abscess, which in 2 of the cases was bilateral, were then treated, bronchial suction being first performed and 100 mg. of elastase in 5 ml. of phosphate solution being then injected into the lobar or segmental bronchus corresponding to the lesion. After 2 to 18 treatments over a period of one week to 3 months all of them became symptom-free. Five other patients, 2 with pneumonia and 3 with purulent bronchorrhoea and extensive pulmonary tuberculosis, were also treated, with similarly satisfactory results. *Kenneth M. A. Perry*

508. **Prophylactic Chemotherapy in Chronic Bronchitis**
E. N. MOYES and S. Z. KALINOWSKI. *Tubercle* [*Tubercle (Lond.)*] **40**, 112–118, April, 1959. 13 refs.

The investigation here reported from the Royal Infirmary, Worcester, consisted essentially in a comparison of erythromycin and tetracycline in the prophylactic treatment of chronic bronchitis. The 93 outpatients who took part in the trial were all under 70 years old, had at least 2 years' history of daily productive cough and dyspnoea throughout the years, and had no other disabling disease. They were divided at random into four different treatment groups as follows: (1) 25 patients who received 1 g. of erythromycin daily for 7 days and thereafter courses of 1 g. daily for 5 days at the first sign of symptomatic deterioration; (2) 22 who received 1 g. of erythromycin for 7 days followed every 4 weeks by 1 g. daily for 5 days; (3) 21 who received tetracycline in the same dosage and according to the same schedule as in Group 1; and (4) 25 who received 1 g. of tetracycline daily for 7 days followed by 750 mg. daily. [Thus Groups 1 and 3 received comparable treatment, while Groups 2 and 4 did not.] In each group the trial lasted for 4 months, starting in November or December, 1957. The groups were of similar composition in respect of age, duration of illness, amount and quality of sputum, and severity of dyspnoea. The assessment of therapeutic effect at monthly intervals was based on the patient's and the doctor's estimates of symptomatic relief, the number and severity of exacerbations, and the loss of working time, and to a lesser extent on the quantity and degree of purulence of the sputum and the degree of dyspnoea.

At the end of 4 months the number of patients who were considered to have obtained material benefit from the treatment was 15 (60%) in Group 4, 10 (48%) in Group 3, 6 (24%) in Group 1, and 5 (23%) in Group 2. Although severe exacerbations were evenly distributed throughout the four groups, the total number of episodes was least in Group 4 and greatest in Group 1, Groups 2 and 3 together occupying an intermediate position. However, the average loss of working time due to bronchitis was only one week in each of the groups treated with tetracycline compared with 3 weeks in each of those treated with erythromycin.

Before treatment *Staphylococcus aureus* was isolated from the sputum in 75% of cases, *Haemophilis influenzae* in 57%, pneumococci in 27%, and β-haemolytic streptococci in 7%. After the initial 7 days' treatment *H. influenzae* had been eliminated in 39% of the cases treated with erythromycin and in 86% of those treated with tetracycline. Of the monthly sputum specimens examined from Group 4, 54% were sterile and *H. influenzae* was isolated from only 6%. Of those from Group 2, 35% were sterile and *H. influenzae* was present in 29%. In Groups 1 and 3 sputum was examined both at the onset of an exacerbation and after a course of treatment; in Group 1 *H. influenzae* was isolated 27 times and persisted after treatment in 15 cases, whereas in Group 3 *H. influenzae* was isolated on only 7 occasions and never after treatment.

It is concluded that erythromycin has no place in the routine management of chronic bronchitis. [This is perhaps a little unfair to erythromycin, since continuous erythromycin therapy was not given a trial.]
K. Zinnemann

509. **Gas-analytical Studies in Severe Pneumonia. Observations during the 1957 Influenza Epidemic**
H. HERZOG, H. STAUB, and R. RICHTERICH. *Lancet* [*Lancet*] **1**, 593–596, March 21, 1959. 2 figs., 23 refs.

Out of 264 patients suffering from severe Asian influenza who were admitted to the University Medical Clinic, Basle, in the autumn of 1957, 125 had pulmonary complications, and gas analytical studies were performed on 22 of these who required tracheotomy or artificial respiration. Of 10 of these patients with a previous history of cardiac or pulmonary illness, 6 survived, whereas of the other 12 patients with no such history, only 4 survived.

Gas analysis, performed on blood obtained from the brachial artery, showed that hypoxia was present on admission in all patients. After administration of oxygen the oxygen saturation rose to normal values in only 3 patients, presumably owing to the presence of massive arteriovenous shunts around poorly ventilated alveoli. There was a close correlation between the degree of hypoxia and survival: thus of 10 patients with an oxygen saturation value of less than 80%, only 2 survived. But even patients with low oxygen saturation values (less than 60%) survived for several days and showed no irreversible damage to vital organs, the most important cause of death being cardiovascular collapse. The carbon dioxide tension was generally depressed, probably because of hyperventilation. Most of the patients with CO_2 retention gave a history of chronic bronchial obstruction. In many cases an arterio-alveolar pCO_2 gradient was observed, suggesting uneven alveolar perfusion. In the cases in which tracheotomy was performed, aspiration of secretions by suction and artificial respiration were useful in raising the oxygen saturation level. *G. M. Little*

Otorhinolaryngology

510. **Cervical and Otolith Vertigo**
S. COPE and G. M. S. RYAN. *Journal of Laryngology and Otology* [*J. Laryng.*] **73**, 113–120, Feb., 1959. 22 refs.

The authors have shown that vertigo occurs in cervical spondylosis, in patients subjected to neck traction, and in cases of trauma involving the ligaments and muscles of the neck. Stretch impulses arise in the neck and play their part in tonic and righting reflexes, the centre for these impulses being the upper cervical cord. Disease in the neck produces an abnormal flow of impulses to the centre, and hence for distribution to the cerebellum and brain as a whole, the mechanism of the vertigo being similar to that produced by a damaged utricle.

In cases of positional nystagmus of benign paroxysmal type, cervical vertigo can be differentiated from otolith disease by means of the " collar test ", which modifies the vertigo and nystagmus occurring on postural change when the neck is the cause, but does not affect the postural reaction when the otolith is at fault. Cervical vertigo is relieved by the wearing of a cervical collar.

H. D. Brown Kelly

511. **Epidermoid Cholesteatoma and Cholesterol Granuloma. Experimental and Human**
I. FRIEDMANN. *Annals of Otology, Rhinology and Laryngology* [*Ann. Otol. (St Louis)*] **68**, 57–79, March, 1959. 15 figs., 29 refs.

On the basis of a study of 770 specimens of bone removed at operations on the mastoid process during the period 1935–56 at the Royal National Throat, Nose, and Ear Hospital, London, and of extensive experiments on guinea-pigs the present author re-examines the question of the histogenesis of cholesteatoma and of the related condition of cholesterol granuloma and discusses their terminology. The cholesteatoma is a cystic structure lined by keratinizing stratified squamous epithelium, its contents consisting of desquamated keratin, often admixed with pus. The presence of squamous epithelium in the middle ear in this condition has been variously attributed to a congenital origin, to immigration from the external auditory meatus through a perforated tympanic membrane, to implantation following a fracture of the temporal bone, and to metaplasia as a result of chronic inflammation, such as occurs elsewhere in the respiratory tract. Although some cholesteatomata are probably congenital, only a small proportion can originate in this way or by implantation. Convincing evidence of immigration of squamous epithelium has been obtained from both experimental and clinical sources, whereas the author has never observed squamous metaplasia in the bulla of the guinea-pig's ear in the course of 600 experimental infections, nor could such metaplasia be induced by the intra-aural application of cholesterol or by the injection of oestrogens. He therefore considers that in most cases the cholesteatoma is produced by invasion of squamous epithelium into the middle ear. He points out that although squamous metaplasia occurs in the lower respiratory tract, such metaplastic cells seldom undergo the keratinization which is always found in a cholesteatoma. In its histopathology the cholesterol granuloma is fundamentally different, being a granulomatous structure resulting from the irritant action of cholesterol crystals deposited at the site of a haemorrhage. It is not a clinical entity, and the use of the term " epidermoid cholesteatoma " is advocated to distinguish the cystic from the granulomatous lesion.

William McKenzie

512. **Secretory Otitis Media and Nasal Allergy**
D. J. WEEKES. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **68**, 748–751, Dec., 1958. 6 refs.

A preliminary report is presented of the treatment of 27 cases of secretory otitis media, 27 of perennial allergic rhinitis, and 12 of seasonal rhinitis with the antihistamine drug promethazine (" phenergan ") in doses of 25 mg. by mouth at bedtime, (together with local vasoconstrictors, systemic chemotherapy, and hyposensitization as indicated).

Of the 27 cases of otitis media, only 2 failed to respond to this treatment, in one of which irradiation of the nasopharynx was needed. In no case was myringotomy performed. [Unfortunately, the criteria of improvement, which is described only as " subjective " or " objective ", are not defined. It is to be hoped that the final report will include details of the hearing of these patients before and after treatment.] In the other two groups subjective and objective improvement was obtained in at least 75% of cases.

F. W. Watkyn-Thomas

513. **A Critical Study of a New Cerumenolytic Agent**
A. C. REINIGER, G. BIALKIN, J. Q. GANT, M. J. ROSNICK, A. J. MONTEBOVI, and A. HALPERN. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **69**, 293–302. March, 1959. 2 figs., 32 refs.

The authors report the results of experimental and clinical trials of " cerumenex ", a new " cerumenolytic agent ", the purpose of which is to soften hard wax and detach it from the epithelium of the external auditory meatus, thus enabling it to be removed without trauma. Cerumenex is a fatty-acid condensate of a protein polypeptide dissolved in propylene glycol. It is claimed that the substance is sufficiently germicidal to prevent cross-infection, that it is non-irritating as indicated by the " rabbit eye irritation test ", and that it is not allergenic. In a clinical trial on 230 subjects the results were " excellent " in 204 cases, " good " in 19, and " poor " in 7.

F. W. Watkyn-Thomas

Urogenital System

514. **The Artificial Kidney**
F. M. PARSONS and B. H. MCCRACKEN. *British Medical Journal* [*Brit. med. J.*] **1**, 740–751, March 21, 1959. 6 figs., 33 refs.

This paper from the Research Unit on Metabolic Disturbances in Surgery of the Medical Research Council, which includes 5 interesting case reports, reviews 20 months' experience with the rotating type of Kolff artificial kidney at the General Infirmary at Leeds. Of 100 patients with renal failure who were referred for treatment, 82 were treated by dialysis without serious complications and in some cases with unquestionable benefit. Initially a high incidence of infection, mainly with tetracycline-resistant staphylococci, caused trouble, but these were brought under control by " reverse barrier nursing " and frequent sterilization of blankets.

The indications for dialysis were " firstly, clinical changes which may presage deterioration, and, secondly, those changes in the blood chemistry that are generally accepted as constituting a hazard to life ". The principal clinical indications were mental disturbance and vomiting which interfered with a conservative oral regimen. The chemical indications included a carbon dioxide combining power of the blood of less than 13 mEq. per litre, a plasma potassium level above 7 mEq. per litre, and a blood urea nitrogen level above 180 mg. per 100 ml. The importance of excluding urinary obstruction is stressed, and also the value of the anabolic steroid norethandrolone in slowing down the rate of protein breakdown in puerperal renal failure.

[This paper cannot be adequately abstracted and should be read in full.] *D. A. K. Black*

515. **Streptomycin Poisoning in Renal Failure. An Indication for Treatment with an Artificial Kidney**
K. D. G. EDWARDS and H. M. WHYTE. *British Medical Journal* [*Brit. med. J.*] **1**, 752–754, March 21, 1959. 7 refs.

This report from Sydney Hospital, Australia, draws attention to the increased danger of vestibular damage from streptomycin in patients with renal failure, and to the possibility of removing by dialysis streptomycin which has already been given. The cases are described of 5 patients who suffered from vertigo or deafness after being given streptomycin while in renal failure, 2 of them after receiving as little as 4 g. of the drug. Tests *in vitro* showed that streptomycin could be dialysed from blood across cellulose tubing, and it was decided that in future any patient with oliguria who had been given more than 1 g. of streptomycin should be treated with the artificial kidney. Five such cases are reported, in none of which did the patient develop toxic effects of streptomycin. Nor did 2 of a further 3 patients mentioned in an addendum, though the third suffered toxic effects in spite of a reduction in the blood concentration of streptomycin from 32 to 17 μg. per ml. by dialysis. The authors [very properly] urge that renal insufficiency should contraindicate the administration of streptomycin. *D. A. K. Black*

516. **Kidney Function during Acute Tubular Necrosis: Clinical Studies and a Theory**
W. H. MERONEY and M. E. RUBINI. *Metabolism: Clinical and Experimental* [*Metabolism*] **8**, 1–15, Jan., 1959. 4 figs., 13 refs.

In 10 patients studied at the Walter Reed Army Medical Center, Washington, D.C., during the oliguric phase of acute tubular necrosis the urine was found to contain a lower concentration of sodium and a higher concentration of potassium than the plasma, and on successive days the urinary sodium level fell and the potassium level rose, so that there was a steep fall in the sodium:potassium ratio in the urine. This ratio was not influenced by correction of the acidosis or of the hypocalcaemia, but its fall was reversed by haemodialysis on a Kolff–Brigham artificial kidney. As the plasma nitrogen level fell with haemodialysis the urinary nitrogen content also fell. Moreover, there was a progressive fall in the sum of the concentrations of sodium and potassium in the urine, this being roughly compensated for by the rise in the urinary nitrogen level, so that the osmolarity of the urine remained approximately the same as that of the plasma.

The authors discuss fully the theoretical implications of these findings. In their view they give no support to the concept that the urine in the oliguric phase of tubular necrosis is an ultrafiltrate of the plasma. They suggest that most of the urine comes from undamaged tubules, since severely affected tubules, blocked by debris and oedema, contribute no urine, while less severely affected tubules still retain some of their function. In the diuretic phase, as tubular obstruction is relieved, many of the severely damaged tubules begin to act as transporting tubules and are unable to deal with the urine adequately. Hence the loss of large quantities of urine and of salts. *T. B. Begg*

517. **Current Status of Therapy in Glomerulonephritis**
L. A. RANTZ. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **170**, 948–951, June 20, 1959.

518. **Mechanisms of Urinary Concentration and Dilution.** [Review Article]
E. LAMDIN. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **103**, 644–671, April, 1959. 1 fig., bibliography.

Endocrinology

519. **The Diagnostic and Therapeutic Value of Thyrotropic Hormone and Heavy Dosage Scintigrams for the Demonstration of Thyroid Cancer Metastases**
B. CATZ, D. PETIT, and P. STARR. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **237**, 158–164, Feb., 1959. 8 figs., 7 refs.

The authors present from the Thyroid Clinic of Los Angeles County Hospital, California, the histories of 8 cases of cancer of the thyroid gland to show the value of administration of thyrotropic hormone in high dosage before making scintigrams, using relatively large doses of radioactive iodine (^{131}I). As much normal and carcinomatous thyroid tissue as possible was first surgically removed, and each patient was then given 10 units of thyrotropic hormone daily for 5 to 7 days. Whole body scanning counts were then performed after a test dose of 1 to 2 mc. of ^{131}I. A treatment dose of 40 to 100 mc. of ^{131}I was next given if any uptake in residual tissue or metastatic sites was demonstrated, or, in cases with previously known metastases, this dose was given even if no uptake occurred; scintigrams were repeated after this treatment dose. All patients were then given desiccated thyroid or thyroxine in doses gradually increasing to a maximum. Patients who had received the therapeutic dose of ^{131}I were re-studied every month, the others every 3 to 6 months.

The detailed descriptions of the 8 cases demonstrate two points: (1) that uptake of ^{131}I by residual or metastatic tissue may often be detected only after millicurie test doses and sometimes only after therapeutic doses; and (2) that it is worth while injecting thyrotropic hormone daily for as long as a week to increase such uptake. This method can be effective even while administration of thyroid hormone continues. The authors suggest that this procedure may lead to more effective treatment with ^{131}I, as well as to better detection of the presence of functioning thyroid carcinomatous tissue.

K. E. Halnan

520. **The Effect of Triiodothyronine and Thyroxine upon the Rate of Release of Thyroid Hormone in Various Thyroid States**
D. E. JOHNSON, D. H. SOLOMON, and M. A. GREER. *Journal of Clinical Endocrinology and Metabolism* [*J. clin. Endocr.*] **19**, 317–329, March, 1959. 7 figs., 18 refs.

It has previously been shown that the administration of thyroid hormone to patients with Graves's disease does not inhibit uptake of iodine by the thyroid gland, although it does so in healthy subjects. In this paper from the University of California, Los Angeles, are presented the results of giving varying doses of triiodothyronine or thyroxine to normal persons, 15 hyperthyroid patients, 2 patients in the euthyroid stage of Graves's disease, and one acromegalic patient with hyperthyroidism.

In the normal subjects the release of thyroid hormone was almost completely inhibited by small doses of these substances, whereas in the hyperthyroid patients of all types even massive doses failed to influence the secretion rate of thyroid hormone. These findings are considered by the authors to support the theory that hyperthyroidism is due to autonomous activity of either the thyroid gland itself or the pituitary gland, and that it is not due to changes in the sensitivity of the hypothalamic–pituitary apparatus.

M. C. G. Israëls

521. **Sporadic Goitre Due to Dyshormonogenesis: Impaired Utilization of Trapped Iodide**
E. M. MCGIRR, J. H. HUTCHISON, and W. E. CLEMENT. *Scottish Medical Journal* [*Scot. med. J.*] **4**, 107–114, March, 1959. 9 figs., 19 refs.

The results of radioactive iodine studies in 5 euthyroid patients suffering from sporadic goitre and congenital deafness are described. Two of these patients were sisters and 2 were siblings.

The thyroid glands showed a marked avidity for ^{131}I. The oral administration of potassium thiocyanate or perchlorate caused an abrupt but partial discharge of the trapped iodide, indicating a defect in the ability to incorporate it into a protein complex. The demonstration by chromatographic analysis of the presence in the thyroid glands removed from 2 patients of iodotyrosines and iodothyronines confirmed the partial nature of the enzyme deficiency.

The euthyroid state of the 5 patients indicated that their enlarged thyroid glands, stimulated by pituitary thyrotrophin, could compensate for their intrinsic deficiency of a specific enzyme. This enzyme deficiency and the deaf-mutism were probably determined by the activity of 2 closely linked genes.—[Authors' summary.]

522. **Subclinical or Latent Adrenal Insufficiency.** (Les insuffisances surrénales infra-cliniques ou frustes)
L. DE GENNES, H. BRICAIRE, and L. MOREAU. *Presse médicale* [*Presse méd.*] **67**, 619–622, March 28, 1959.

The clinical diagnosis of adrenal insufficiency usually presents no difficulty, and the clinical signs can be confirmed by the results of chemical and biological tests and by the successful outcome of hormone therapy. In a number of cases, however, the disorder does not at once produce characteristic symptoms, but exists in a subclinical or incipient form for a considerable period of time, during which its presence is usually unsuspected, until it is suddenly revealed by some unwonted stress brought about by for example acute infection, trauma, or surgery. Such instances have been known for half a century—they were mentioned by Sergent and Bernard as early as 1903—but have been largely overlooked.

The present authors report 10 cases in which they observed this sudden and dangerous manifestation of pre-

viously unsuspected adrenal dysfunction, usually as a result of surgical intervention. Determination of the urinary 17-ketosteroid and 17-hydroxycorticosteroid levels and the application of Thorn's test then revealed the presence of adrenal failure. The taking of a careful history then showed that in 6 of these cases clinical signs had indeed been present, but were so slight that due attention had not been paid to them. The most frequent early signs are anorexia, emaciation, and debility, but these are of course not specific for adrenal dysfunction. The authors suggest that if these signs or slight pigmentation of the skin are observed in patients about to undergo surgery a test of adrenal function should be carried out. They have noted an association between tuberculosis and adrenal disease. Determination of urinary 17-ketosteroid and 17-hydroxycorticosteroid excretion in the present cases showed that they could be divided into two types: (1) those in which the urinary steroid level was rather low but responded to stimulation with ACTH; and (2) those in which the urinary steroid level was low or normal but failed to respond to ACTH. *Nancy Gough*

DIABETES MELLITUS

523. **Proliferative Retinopathy in Diabetes Mellitus. Review of Eight Hundred Forty-seven Cases**
H. F. Root, S. Mirsky, and J. Ditzel. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **169**, 903–909, Feb. 28, 1959. 4 figs., 17 refs.

At the Joslin Clinic and the New England Deaconess Hospital, Boston, the authors have reviewed the records of 847 diabetic patients (379 men and 468 women) with proliferative retinopathy seen during the period 1928–57. During these 30 years 331 of the patients had died.

In 707 cases (83·6%) the diagnosis of proliferative retinopathy was made before the age of 60 and in only 14 (1·7%) was it made under the age of 20 years. The diabetes had been diagnosed before the age of 20 years in 351 (42%) of the cases and in only 12 (1·4%) after the age of 60, though in many of these the actual onset of the disorder may have been several years earlier. The duration of the diabetes at the time of the diagnosis of proliferating retinopathy varied between 1 and 29 years, with an average of 17·6 years. The dosage of insulin varied considerably, but the majority of patients had required more than 25 units per day; only 22 (2·6%) had not received any insulin at all. In a large majority of cases a long period of indifferent control of the diabetes had preceded the onset of proliferative retinopathy, and in no case was there a history of early diagnosis and continued meticulous control. In 40% of the patients albuminuria had been present for some time before the diagnosis of proliferative retinopathy and in later years diabetic nephropathy was almost invariably associated with the proliferative retinopathy.

The duration of life after the recognition of proliferative retinopathy was very variable; thus 309 patients died in less than 10 years, while 16 survived for 15 years or more. It was known that 147 (44·5%) of these patients died of diabetic nephropathy and 124 (37·4%) of arteriosclerotic heart disease, the former cause of death being commoner in younger patients and the latter in the older, but 32 patients under the age of 39 years died of coronary occlusion. No patient under 20 years of age died. In the last 206 consecutive cases in the series the incidence of blindness in the age groups 20–39, 40–59, and 60+ was 29·7, 23·0, and 29·0% respectively, but no patient under the age of 20 years was blind. The authors suggest that this analysis shows that diabetic retinopathy occurs predominantly in young and middle-aged adults who have had diabetes for an average of 17 years. It does not support the assumption that simple and proliferative retinitis are two fundamentally different ocular disorders. *Charles Rolland*

524. **Significance of Effectiveness of Combined Insulin–Orinase Treatment in Maturity-onset Diabetes**
B. W. Volk and S. S. Lazarus. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **237**, 1–7, Jan., 1959. 2 figs., 31 refs.

It is probable that the hypoglycaemic effect of the sulphonylureas is due to their ability to increase the output of insulin by the pancreas. Thus, it has been observed that only in diabetics with some degree of pancreatic insulinogenic reserve can a satisfactory hypoglycaemic effect be expected from the administration of these substances. Clinically, it is patients with diabetes with onset in maturity in whom the response is most satisfactory, and it is suggested that these patients still have such pancreatic reserve, but possibly have some defect in the normal mechanism for controlling the blood sugar level, in which hyperglycaemia acts by increasing insulin output.

The present authors report from the Jewish Chronic Disease Hospital, Brooklyn, New York, the results of a study undertaken to determine whether the combined use of "orinase" (tolbutamide) and insulin was more effective than either preparation alone. In the 12 patients studied, who were aged between 52 and 75 years, the duration of the diabetes ranged from 9 to 34 years. Many of them had diabetic vascular complications, and all had previously been taking at least 30 units of insulin daily. The fasting blood sugar level was usually greater than 200 mg. per 100 ml. After 2 weeks of observation the dose of insulin was reduced by 30% while at the same time 0·5 g. of tolbutamide was added twice daily. After 3 to 6 weeks the insulin was gradually withdrawn completely, the patients being maintained on tolbutamide, 1 g. twice daily, for several weeks, when insulin was again introduced in addition to the tolbutamide. In all the patients who received a reduced amount of insulin along with 1 g. of tolbutamide the average fasting blood sugar level decreased to below 160 mg. per 100 ml.; however, when insulin was subsequently completely withdrawn the fasting blood sugar level tended to rise to the previous levels. In some cases it was noted that the response to tolbutamide alone was better than the response to insulin alone.

The authors suggest that the synergistic effect of tolbutamide and insulin demonstrated in these cases may

be explained by the theory that the sulphonylureas exert their hypoglycaemic effect primarily through their pancreatotrophic action. They suggest that the administration of exogenous insulin " puts the pancreas at rest ", while the simultaneously administered tolbutamide stimulates the production of endogenous insulin in those patients who still have adequate insulinogenic reserve. It seems likely that in these patients the diabetic state results from a defect in the normal mechanism for controlling the blood sugar level. *John Lister*

525. **Preliminary Clinical Observations on the Use of a Biguanide (DBI) as an Oral Hypoglycemic Agent**
C. WELLER and A. MACAULAY. *Journal of the American Geriatrics Society* [*J. Amer. Geriat. Soc.*] **7**, 128–135, Feb., 1959. 1 fig., 13 refs.

The effect of a new oral, non-sulphonamide, hypoglycaemic compound, N-beta-phenylethyl formamidinyliminourea (DBI), a biguanide, has been studied at Grasslands Hospital, Valhalla, New York, in 42 unselected diabetic patients in whom dietary control alone was inadequate. The least dose of DBI was 25 mg. three times a day by mouth, increasing to the limit of tolerance or until the blood sugar level returned to normal. Of these patients 27 (65%) responded with a fall in blood sugar level, although 5 suffered from nausea or vomiting; the other 15 (35%) did not respond. The criteria of improvement included a 30% reduction in the blood sugar level and the ability of DBI to replace insulin to the extent of 50% or more of the previous dose, even in patients requiring large doses; this latter criterion was fulfilled in 16 cases. No organic toxic effects were noted over periods of one to 6 months. This new biguanide is considered to be an effective hypoglycaemic agent which, in spite of its side-effects, promises to be of clinical value. *Kenneth Gurling*

526. **" Plasma Insulin Activity " in Human Diabetes during Hypoglycemic Response to Tolbutamide and Indole-3-acetic Acid**
H. S. SELTZER and W. L. SMITH. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol. (N.Y.)*] **100**, 171–174, Jan., 1959. 14 refs.

The authors, working at the University of Texas Southwestern Medical School and the Veterans Administration Hospital, Dallas, Texas, have investigated the hypoglycaemic action of tolbutamide and indole-3-acetic acid by studying the " insulin activity " of the circulating blood before and after administration of the drugs to normal and diabetic subjects. The plasma insulin activity was estimated by the Vallance–Owen rat-diaphragm technique, in which the glucose uptake from the plasma by one hemidiaphragm is compared with the uptake from a buffered glucose solution by a control hemidiaphragm.

Three groups were studied: (1) 5 normal individuals; (2) 7 elderly diabetics whose disease was easily controlled by diet and tolbutamide; and (3) 5 labile juvenile diabetics who promptly developed ketosis on withdrawal of exogenous insulin. In Group 3 the insulin dosage during the experiment was reduced to the minimum needed to prevent frank ketosis. On the first test day blood samples for determination of the glucose content and plasma insulin activity were taken from the fasting patient and again one hour after the administration of 100 g. of glucose by mouth. On the next day indole-3-acetic acid in a dose of 100 mg. per kg. body weight or tolbutamide in a dose of 3 g. was given to the fasting patient, the blood glucose level being determined at hourly intervals for 5 hours and the plasma insulin activity about 2 to 3 hours after administration of the drug.

The hypoglycaemic effects of the two drugs were similar, being virtually absent in Group 3, slight in Group 1, and marked in Group 2. The results of assay of the plasma insulin activity in the fasting state were similar to those observed by other workers, no activity being apparent in Group 3 and significant amounts in Groups 1 and 2, the activity in the latter being very slightly less than in the former. After the administration of 100 g. of glucose there was a significant increase in the plasma insulin activity in Groups 1 and 2, but none in Group 3. After the administration both of indole-3-acetic acid and of tolbutamide there was no demonstrable increase in plasma insulin activity in any of the three groups.

Thus both tolbutamide and indole-3-acetic acid appear to act only in the presence of insulin in the peripheral blood, but neither increases the amount of circulating insulin. To explain these findings it is suggested that the drugs act by augmenting intrahepatic insulin activity —either by stimulating the β cells of the pancreas to release insulin which is largely bound to the liver cells in the post-absorptive state (tolbutamide) or by inhibiting insulinase, the highest concentrations of which are found in the liver (indole-3-acetic acid)—thus causing hypoglycaemia without enhanced insulin activity in the peripheral blood. *T. D. Kellock*

527. **The Mechanism of Insulin Antidiuresis**
H. V. MURDAUGH, R. R. ROBINSON, and E. M. DOYLE. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **53**, 569–571, April, 1959. 1 fig., 5 refs.

At Duke University Medical Center, Durham, North Carolina, water diuresis was induced in the fasting state in 13 normal subjects and in 2 patients with diabetes mellitus and " heavy glycosuria ". After a control period, during which urine collections were made, 0·15 to 0·2 units of hyperglycaemic-factor-free (H.G.F.) insulin was given rapidly into an antecubital vein.

It was shown that the insulin had an antidiuretic effect in all these individuals, and further that in all of 6 of the normal subjects tested this effect could be inhibited by the intravenous administration of absolute alcohol, which has been reported to inhibit the release of antidiuretic hormone from the posterior lobe of the pituitary. Insulin had no antidiuretic effect in one additional patient with diabetes insipidus who was responsive to vasopressin. It is concluded that the diuresis induced by insulin is mediated through the action of antidiuretic hormone released by it and not by a direct action of the insulin on the renal tubule, as has previously been suggested. *F. W. Chattaway*

The Rheumatic Diseases

528. **Laboratory Investigations in the Diagnosis of Rheumatic Diseases**
J. H. GLYN and M. IRVING. *Annals of Physical Medicine* [*Ann. phys. Med.*] **5**, 1–9, Feb. [received April], 1959. 26 refs.

A number of non-specific, " acute phase " serological tests indicative of inflammatory disease have in recent years been compared with the erythrocyte sedimentation rate (E.S.R.) and some of them recommended for clinical use. In this communication from the Prince of Wales and Edgware General Hospitals, London, the authors report the results of a clinical evaluation of some of these tests, which they consider would be sufficiently simple for routine clinical use in separating significant from insignificant rheumatic disease. These included estimation of serum levels of C-reactive protein, total protein-bound polysaccharides, mucoprotein polysaccharides, total protein, and the serum protein:polysaccharide ratio, the results being compared with the E.S.R. as determined by the Westergren method. In all, a total of 455 tests were performed on 330 patients.

In 30% of 91 cases of active rheumatoid arthritis the E.S.R. was normal, whereas in only 3·5% of these cases were the results of the newer tests within normal limits. In one group of 73 cases in which the diagnosis was at first uncertain, but later became clear, 35 proved to be cases of rheumatoid arthritis; in this group the newer tests were found to be less reliable than the E.S.R.

The authors conclude as follows: (1) in established rheumatoid arthritis and ankylosing spondylitis—conditions in which laboratory tests are not much needed—the newer tests give fewer false negative readings than the E.S.R.; (2) as a measure of disease activity in cases not receiving drug treatment they are as accurate as the E.S.R.; but (3) as a help in solving diagnostic problems in rheumatic disease they are disappointingly unreliable. The Winzler mucoprotein test was slightly more reliable than the others. As these tests are time-consuming they cannot justifiably be recommended. *Kenneth Stone*

529. **Resorption of Intracutaneously Injected Congo Red**
R. A. PARKINS and E. G. L. BYWATERS. *Annals of the Rheumatic Diseases* [*Ann. rheum. Dis.*] **18**, 8–14, March, 1959. 3 figs., 7 refs.

It has been found that the stain produced by intracutaneous injection of Congo red dye disappears more slowly in patients with rheumatoid arthritis, especially juveniles, than in controls. The rate of fading of this stain was studied in 66 patients with rheumatoid arthritis and 96 controls, most of whom were in-patients at Hammersmith Hospital, London. In adult rheumatoid arthritis the fading rate did not differ significantly from that in healthy subjects and was not influenced by age, disease activity, or treatment with steroids. There was delay in fading in the 8 patients with systemic lupus erythematosus (all of whom were receiving steroid hormones), in one patient with chronic discoid lupus erythematosus, in 5 out of 7 with secondary amyloidosis (in 5 this was secondary to rheumatoid arthritis), and in 10 out of 13 with hepatocellular or obstructive jaundice. Histological examination of a skin biopsy specimen from the injection site in one patient with amyloidosis failed to reveal local amyloid deposits. *M. Wilkinson*

530. **A Simple Precipitation Reaction for the Qualitative Study of the Rheumatoid Factor.** (Eine einfache Präcipitationsreaktion zum qualitativen Nachweis des " Rheumafaktors ")
W. MÜLLER. *Klinische Wochenschrift* [*Klin. Wschr.*] **37**, 86–91, Jan. 15, 1959. 1 fig., 13 refs.

From the Medical Clinic of the University of Freiburg the author reports the evaluation of a quick and simple method of demonstrating the presence of rheumatoid factor in serum. The test is called the capillary precipitation test (C.P.T.). The antigen employed is a commercial solution of human γ globulin (16%) diluted with borate–saline buffer and heated at 63° C. for 30 minutes, a procedure which is believed to result in molecular aggregation. The patient's serum is not inactivated. Serum and γ-globulin solution are drawn up successively into a glass tube 8 cm. long and of about 5 mm. bore, care being taken to avoid the inclusion of an air-bubble between them. After 2 hours' incubation at 37° C. the tubes are refrigerated overnight and examined for precipitate at the point of contact of the two fluids. This test was carried out in parallel with the Rose–Waaler haemagglutination test, the latex fixation test of Singer and Plotz, and the author's " boundary layer reaction " (*Z. Rheumaforsch.*, 1958, **17**, 206). This last test is similar to the C.P.T., but is stated to be capable of providing a quantitative result; it employs heated γ globulin at 0·5% concentration and the patient's serum is diluted 1:6. Sera from 224 patients with various rheumatic disorders, 40 patients with non-rheumatic inflammatory disease, and 20 healthy subjects were examined.

In rather more than 75% of cases the result of the C.P.T. agreed with those of the other tests. In 16% of cases the result of the C.P.T. was negative when all 3 other tests gave a positive reaction, while very rarely the C.P.T. gave a positive result when the results of the other tests were negative—this usually occurred with the serum of patients who were probably not suffering from rheumatoid arthritis. The C.P.T. tended to give negative results in cases in which the titre of rheumatoid factor by the haemagglutination and latex fixation tests was low. Some correlation between the amount of precipitate formed and the titre of the latex fixation test was obtained when the γ-globulin concentration employed was 2·5%; with strengths of 5% or more, however, false positive results were obtained.

It is concluded that this test cannot at present replace the more elaborate reactions usually employed in testing for the rheumatoid factor. *G. Loewi*

531. **Synovial Fluid Hyaluronate in Rheumatoid Arthritis**

D. HAMERMAN and H. SCHUSTER. *Arthritis and Rheumatism* [*Arthrit. and Rheum.*] **1**, 523–531, Dec., 1958. 13 refs.

The polysaccharide hyaluronate is the main cause of the viscosity of synovial fluid. This substance, a polymer of N-acetyl glucosamine and glucuronic acid, can be measured indirectly by determining the hexosamine content of synovial fluid or mucin clot. However, hexosamines also exist in combination with other synovial fluid proteins. The authors, working at the Albert Einstein College of Medicine, New York, have analysed 19 specimens of synovial fluid from 13 patients with rheumatoid arthritis and 10 specimens from normal knees (8 of these being obtained post mortem), and determined the hyaluronate content by two independent methods; (1) precipitation of hyaluronate as a mucin clot by acetic acid, followed by determination of the hexosamine in the clot; and (2) by measuring the fall in hexosamine level in the fluid following hyaluronidase digestion and dialysis *in vitro*. Control experiments showed that the hexosamine in mucin clot was derived solely from hyaluronate and that only hyaluronate hexosamine was rendered dialyzable by hyaluronidase.

The results of the two methods agreed. The hyaluronate hexosamine content of rheumatoid synovial fluid of greater than normal volume (measured by weight) averaged 0·4 mg. per gramme and constituted 30% of the total fluid hexosamine content. In normal synovial fluids these values were 1·4 mg. per gramme and 85% respectively. Rheumatoid and normal synovial fluids diluted to equal concentrations of hyaluronate hexosamine were shown to have similar viscosities (by the Ostwald method). It is suggested that dilution of hyaluronate, rather than depolymerization, seems to be the main cause of the low viscosity of synovial fluid in rheumatoid arthritis. *Allan St. J. Dixon*

532. **Relaxin ("Releasin") Therapy in Diffuse Progressive Scleroderma. A Preliminary Report**

J. A. EVANS. *A.M.A. Archives of Dermatology* [*A.M.A. Arch. Derm.*] **79**, 150–158, Feb., 1959. 4 figs., 10 refs.

In a previous study of the results of all forms of treatment of diffuse progressive scleroderma the author and colleagues found that extensive sympathectomy resulted in palliation in about 88% of patients. In an attempt to help these patients still further the present author, at the Lahey Clinic, Boston, tried administration of relaxin, a polypeptide-like ovarian hormone which occurs most abundantly during pregnancy. To a series of 11 patients (9 female and 2 male) who had been subjected to sympathectomy for widespread scleroderma relaxin was given intravenously for "3 to 7 days in increasing doses from 2·5 mg. to 80 mg. in 5% dextrose and saline solution", and then intramuscularly in a dosage of 30 mg. to 50 mg. 2 to 7 times a week. Subsequently 4 of the patients received daily a rectal suppository containing 40 mg. All the patients were given in addition 1 mg. of diethylstilboestrol daily throughout the trial.

In general there was greater flexibility of the skin in 8 of the 11 cases treated for 7 to 23 months, the hands showing least improvement. Soreness at the injection site was common and in 2 patients a local allergy to the injections developed, which was controlled by hydrocortisone. One patient had a fatal anaphylactoid reaction when an intravenous injection was repeated after suppositories had been used.

A further 2 patients received relaxin before sympathectomy: one became progressively worse, showing no improvement after the operation, and died from anaphylaxis; the other showed improvement only after operation. In a group of 6 patients treatment was begun some months after operation; in 4 of these there was definite improvement in sclerodermatous skin areas; the remaining 2 patients died—one some time later from a ruptured oesophagus and one from an unknown cause. Of 3 cases in which relaxin was given immediately after operation there was notable improvement in one and some improvement in non-sympathectomized areas in one; the third patient died after 4 months. Dysphagia was relieved in 4 out of 8 patients with oesophageal scleroderma. Healing of long-standing ulcers of the leg was complete in 2 out of 3 patients, while the third patient benefited considerably from the treatment.

Benjamin Schwartz

533. **Scleroderma of the Lungs**

R. D. MILLER, W. S. FOWLER, and F. H. HELMHOLZ. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] **34**, 66–75, Feb. 4, 1959. 3 figs., 9 refs.

This paper records the results of a study at the Mayo Clinic of the pulmonary function in 22 (9 male and 13 female) patients aged between 28 and 75 years with scleroderma. The first symptoms of the disease had occurred 4 months to 15 years (average 3·3 years) before this examination. The chief complaint referable to the lungs was exertional dyspnoea in 15 cases and cough in 3; in 2 patients there was also emphysema which, however, was probably unrelated. Radiography of the chest showed no significant amount of fibrosis in 8 cases, slight localized fibrosis in 2, moderate generalized fibrosis in 2, and severe generalized fibrosis in 10; this was usually most prominent in the lower half or two-thirds of the lung fields. The severity of pulmonary fibrosis was not always proportional to the degree of sclerodermatous involvement of the skin.

Pulmonary function tests showed that total lung capacity was usually reduced in the presence of radiological fibrosis. Vital capacity was reduced in all the patients, with or without radiological signs, in no case exceeding 63% of normal. Residual volume was reduced only in those with severe pulmonary fibrosis. Arterial blood oxygen saturation was reduced in one of the patients with emphysema and in 2 with severe generalized fibrosis. Hypoxaemia after exercise occurred in most of the patients with generalized pulmonary fibrosis.

G. Loewi

Physical Medicine

534. **The Effect of Contrasts of Temperature on the Body.** (Контрастные температуры и их влияние на организм)
N. I. Bobrov. *Гигиена и Санитария* [*Gig. i Sanit.*] **23**, 26–31, Dec., 1958. 7 refs.

In this investigation of the effects of prolonged exposure of the human body to contrasting temperatures, which was undertaken in order to determine what bearing such a procedure might have on forecasting the ability to acclimatize persons about to proceed to places with rapid changes of climate, observations were made on three groups of male human subjects, of which one was exposed to contrasting temperatures in the form of alternate hot and cold shower baths for a few minutes each day, the second was exposed to cold air for similar periods, and the third acted as a control group. The indices which were used to detect the development of adaptation of the individual to the contrasts of temperature were: (1) a reduction in the fall of skin temperature during cooling, (2) the increase in the gas exchange during the time of action of the contrast procedure as compared with that preceding its action, and (3) the absence of any marked change in the sensory and motor chronaxies in the part of the body exposed to cooling.

From the results obtained the author concluded that the prolonged action of contrasting temperatures in the form of systematically repeated exposure to cold produces a gradual adaptation of the body towards the procedure. He suggests that as a method of increasing the resistance of the body, these contrast procedures could be employed for prophylactic purposes in districts with unfavourable climatic conditions. Since the most irregular and greatest variations of temperature occur in the spring, it is recommended that the method be used shortly before this season of the year. *Basil Haigh*

535. **Clinical Method of Assessing Tonus and Voluntary Movement in Hemiplegia**
J. B. Brennan. *British Medical Journal* [*Brit. med. J.*] **1**, 767–768, March 21, 1959. 11 refs.

Examining hypertonic muscle groups presents difficulties which are not encountered in the examination of normal or flaccidly paralysed muscles. Chief of these is the influence upon the clinical findings of certain factors such as temperature, emotion, attitudinal reflexes, and synergy movements. Unless the effect of each of these is strictly and uniformly standardized the examination findings will not be a true reflection of change in tonus or active movement.

A method of clinical examination is described which is thought capable of providing accurate information regarding change, spontaneous or as a response to treatment, in the tonus and contractility of muscle groups presenting tonic spasm and motor deficit.—[Author's summary.]

536. **A Study of Contractures in Muscular Dystrophy**
K. C. Archibald and P. J. Vignos. *Archives of Physical Medicine and Rehabilitation* [*Arch. phys. Med.*] **40**, 150–157, April, 1959. 2 figs., 6 refs.

At the University Hospitals of Cleveland, Ohio, 43 patients with muscular dystrophy were observed over a period of 3 years. It was found that these patients developed contractures which affected all the joints, the most prominent contractures being in the iliotibial band, the hamstrings, and the gastrocnemius muscles. The authors consider that contractures of the iliotibial band are particularly important and difficult to treat. Another factor leading to early contracture was muscle imbalance between agonist and antagonist. There was a direct correlation between the degree of co-operation in carrying out exercises, including stretching exercises in the home, and success in preventing contractures. The results obtained with splints in these cases were disappointing but the fitting of correct braces helped to delay the development of contracture.

The authors state that all those patients who conscientiously carried out a programme of exercises and stretching continued to be ambulatory. They emphasize that a wheel-chair is difficult to discard once it has been used for more than a few weeks. *W. Tegner*

537. **Electromyographic Composition of Poliomyelitis-injured Muscle**
E. F. Adams and G. C. Knowlton. *Archives of Physical Medicine and Rehabilitation* [*Arch. phys. Med.*] **40**, 99–104, March, 1959. 1 ref.

At the Institute of Physical Medicine and Rehabilitation, Warm Springs, Georgia, 132 muscles in patients who had suffered from paralytic poliomyelitis 3 months to 15 years previously were examined by electromyography in order to compare the electrical activity with voluntary muscle power. Grades of muscle strength according to the scale of Lovett were combined to give 6 groups. The tests were confined to the rectus femoris, the anterior tibial, gastrocnemius, and the long peroneal muscles, each muscle being tested at 60 points with a coaxial needle, and the findings graded on a points scheme. The results are presented statistically and are analysed.

The authors conclude that electromyography is useful in prognosis, since a muscle showing either voluntary or polyphasic potentials should recover some power. They describe a "polyphasic index", that is, the ratio of polyphasic potentials to the total number of pathological potentials, and state that when this ratio is greatest the muscle strength will be good. The presence of fibrillation potentials or of silent areas indicated a poor prognosis.

The significance of the results is discussed at considerable length. *J. B. Millard*

Neurology and Neurosurgery

538. **Control of Intractable Pain in Advanced Cancer by Subarachnoid Alcohol Block**
R. C. HAY, T. YONEZAWA, and W. S. DERRICK. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **169**, 1315–1320, March 21, 1959. 4 figs., 12 refs.

Although intractable pain due to malignant disease may be relieved by intrathecal injection of absolute alcohol, experience has shown that muscle paralysis, bladder and intestinal disturbances, and painful paraesthesiae may occur as a result of this procedure. These complications can be avoided, however, if adequate precautions are taken to limit the action of the alcohol to the dorsal nerve roots, and the present authors describe a technique of subarachnoid alcohol block which was employed in 106 patients with malignant disease at the M. D. Anderson Hospital, Houston, Texas. Pain was completely relieved in 53 patients and partially relieved in 35. The effect was poor in 11 patients while 7 did not obtain any relief from pain. The average duration of effect was some 3 or 4 months. The only complication reported was transitory incontinence of urine in one patient. *A. G. Freeman*

BRAIN AND MENINGES

539. **The Phenomenon of Visual Perseveration. Its Localizing Value for Occipital Lesions.** (Le phénomène de persévération visuelle. Sa valeur localisatrice pour les lésions occipitales)
J. LE BEAU and E. WOLINETZ. *Revue neurologique* [*Rev. neurol.*] **99**, 524–534, Nov., 1958 [received March, 1959]. 4 figs., 6 refs.

The authors report from the Hôpital Lariboisière, Paris, the case of a man aged 64 years who had a 2-years' history of right-sided optic atrophy and who later developed a left homonymous hemianopia. During the 2 weeks before admission the patient, who was extremely intelligent, had observed that while reading the last letters of one line of print appeared to be superimposed upon the beginning of the next line for about 2 seconds, and that objects such as vehicles moving from left to right were followed by a clear reproduction of their image which persisted for one or 2 seconds. Similarly one part of a panorama remained superimposed upon his view when he looked in another direction. At operation an astrocytoma was removed from the right occipito-temporal region.

The authors review 3 similar cases previously described by themselves (*Rev. neurol.*, 1952, **86**, 692) and 7 cases reported by Critchley (*Brain*, 1951, **74**, 267; *Abstr. Wld Med.*, 1951, **10**, 648). It is concluded from these and the case herein reported that the phenomenon of visual perseveration is a valuable aid in the localization of occipital lesions. *I. Ansell*

540. **Paget's Disease of the Skull and Secondary Basilar Impression**
J. W. D. BULL, W. L. B. NIXON, R. T. C. PRATT, and P. K. ROBINSON. *Brain* [*Brain*] **82**, 10–22, March, 1959. 6 figs., 41 refs.

In this paper from the Institute of Neurology, Queen Square, London, a detailed study is reported of the appearances of the base of the skull in lateral radiographs obtained from 64 patients with Paget's disease. Basilar impression occurred in 20 cases and was found to be unrelated to the severity of involvement of the skull as a whole. Four measurements relating the basilar angulation to the foramen magnum were made and the patients were grouped first according to the severity of the disease process and then according to the figures obtained by measurement. It was found that the figures for the basal angle (α) alone were not sufficient to indicate the severity of the disease process. Figures for the angle (β) between the plane of the hard palate and the plane of the atlas vertebra [see Bull *et al.*, *Brain*, 1955, **78**, 229; *Abstr. Wld Med.*, 1956, **19**, 85] increased with the severity of the process. The most satisfactory criterion, however, was measurement of the angle β combined with the measurements proposed by Chamberlain and McGregor (not defined in this paper).

The neurological disturbances produced by compression and distortion of the neuraxis in 4 cases are briefly discussed. *J. B. Cavanagh*

541. **Life-table Analysis of Survival after Cerebral Thrombosis—Ten-year Experience**
R. W. ROBINSON, W. D. COHEN, N. HIGANO, R. MEYER, G. H. LUKOWSKY, R. B. MCLAUGHLIN, and H. H. MACGILPIN. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **169**, 1149–1152, March 14, 1959. 4 figs., 7 refs.

The records were reviewed of 1,018 patients admitted to two hospitals in Worcester, Massachusetts, with cerebral thrombosis between 1947 and 1956, and of 97% of the survivors successfully followed up.

The initial mortality was 21%. Of the 737 survivors 15% had died at the end of the first year compared with an expected mortality of 5%; at the end of 4 years the mortality was 50%, the expected rate being 18%; and at the end of 5 years 59% of the survivors had died compared with an expected rate of 23%. Although the initial mortality was higher in women than in men, no differences in long-term mortality were noted. The principal causes of death in patients surviving the initial attack were recurrent cerebrovascular disease and other vascular disorders, which together accounted for 85% of all deaths. There were no important differences between those who survived and those who did not survive the initial attack in regard to the incidence of coronary disease, diabetes mellitus, or hypertension. Three fac-

tors that adversely affected the prognosis were associated congestive heart failure, a more severe initial attack, and early recurrence. *John Fry*

542. **Treatment of Narcolepsy with " Ritalin "**
R. E. Yoss and D. Daly. *Neurology* [*Neurology (Minneap.)*] **9**, 171–173, March, 1959. 2 refs.

At the Mayo Clinic methyl phenidate hydrochloride (" ritalin ") has been given to 60 patients suffering from narcolepsy, including most of the 25 patients who were the subject of a previous study (*Proc. Mayo Clin.*, 1956, **31**, 620; *Abstr. Wld Med.*, 1957, **21**, 346). The dosage of the drug, which was given 30 to 45 minutes before meals, was 20 mg. 3 times a day initially, increased subsequently until symptoms were relieved or troublesome side-effects appeared. The largest daily dose was 300 mg. Good relief was experienced in respect of abnormal sleepiness by 49 patients, and 15 out of 27 suffering from cataplexy were improved. Sleep paralysis and hypnagogic hallucinations were not influenced by the drug. Side-effects, which were noted by more than half the patients, included nervousness, anorexia, insomnia, tachycardia, and skin rash. In the earlier trial 84% of patients were improved by ritalin; over two-thirds of these reported good results after prolonged use.
J. B. Stanton

543. **Some Observations on Occipital Epilepsy.** (Considérations sur l'épilepsie occipitale)
J. E. Paillas, R. Vigouroux, G. Darcourt, and R. Naquet. *Neuro-chirurgie* [*Neuro-chirurgie*] **5**, 3–16, Jan.–March, 1959. 4 figs., 11 refs.

Observation of the apparent paradox that epilepsy with visual aura and evidence of occipital discharges is more common in cases showing no evidence of a lesion in the occipital lobe than in cases in which there is known to be such a lesion led the authors to analyse 30 cases known to have lesions limited to the occipital lobes which were seen at the Neurological Clinic of the Faculty of Medicine, Marseilles, between 1946 and 1958. In 18 of these patients the lesion was not epileptogenic, but in the remaining 12 (9 males and 3 females) symptomatic epilepsy was present; in these patients, whose ages ranged from 4 to 48 years, the lesions included abscess, tumour, angioma, haematoma, softening of the brain, and cortical cicatrice. Of 11 of the 12 patients examined visual field defects were present in 9.

On the basis of this material the authors discuss the epileptic potentiality of the occipital lobes, pointing out that although these lobes are subject to lesions with the same frequency as other parts of the brain, analysis of the present and other reported series of occipital lobe tumours shows that a much smaller proportion of these tumours are epileptogenic than of tumours situated elsewhere in the cerebral hemisphere. Paradoxically, however, epilepsy accompanied by a visual aura and occipital discharges in the absence of an occipital lobe lesion is fairly common, as was shown by Gastaut, who among 50 cases of occipital-lobe epilepsy without a lesion found only 5 with an occipital-lobe lesion. Discussing possible explanations of this paradox the authors draw attention to the fact that visual attacks may be followed by manifestations of involvement of the Rolandic or temporal areas. On the other hand visual attacks never follow motor or temporal-lobe attacks, suggesting that the direction of spread of the convulsion is always from behind forwards, so far as the occipital lobe is concerned. They also point out that the visual attacks are not immediately followed by a generalized seizure, and that if the latter does occur, it is preceded by psychomotor symptoms, clonic movements, or paraesthesiae before becoming generalized, this observation suggesting that the propagation is primarily cortical and only secondarily involves the basal elements of the brain.

The authors conclude by dividing cases of occipital-lobe epilepsy into three groups: (1) those in which there is a detectable macroscopic lesion, such as a scar, tumour, or angioma; (2) those without an occipital lesion in which visual attacks appear to be induced from epileptic foci situated at a distance, usually in the anterior temporal region; and (3) mixed cases in which, while they appear to be functional, there are in fact microscopical lesions, possibly ischaemic in nature, at the anterior external boundary of the occipital lobe. These three groups may present identical clinical pictures and their differentiation depends on the discovery of persistent visual-field defects in the cases with macroscopical lesions, and the use of radiological and electroencephalographic methods of investigation. *J. B. Stanton*

544. **Chemopallidectomy and Chemothalamectomy for Parkinsonism and Dystonia**
I. S. Cooper. *Proceedings of the Royal Society of Medicine* [*Proc. roy. Soc. Med.*] **52**, 47–60, Jan., 1959. 11 figs., 15 refs.

This paper is based upon a review of 850 patients with Parkinsonism and other disorders occasioning involuntary movements in whom lesions of the globus pallidus and thalamus were induced surgically at St. Barnabas Hospital, New York. The lesions were at first produced by occlusion of the anterior choroidal artery, which was thought to produce infarction of the medial globus pallidus and the ventrolateral thalamus as well as their connexions. This procedure was carried out on 55 patients, and striking relief of tremor, rigidity, and deformity was obtained in the successful cases. Because of anatomical variations in the anterior choroidal artery and doubts as to adequacy of collateral circulation in the internal capsule following its occlusion in the elderly patient, however, it was considered that the routine employment of this technique would be unwise, and the production of lesions in the same territory by instillation of alcohol was investigated. The method employed is as follows. Following pneumoencephalography, and with the posterior margin of the foramen of Monro as the most important landmark, a polyethylene cannula is passed into the medial globus pallidus or ventrolateral thalamic area. Distension of an inflatable balloon at its tip provides physiological confirmation of the correct placement of the cannula and is followed by injection of alcohol into the cavity so created. The cannula remains *in situ* so that sub-

sequent enlargement of the lesion is possible if required. The results of chemopallidectomy by this method were favourable in 70% of cases, rigidity being relieved in 80% and tremor in 60%. The author now favours a lesion placed more posteriorly in the treatment of tremor and rigidity (chemothalamectomy). This lesion relieves tremor and rigidity in 90% of properly selected cases and the relief is said to be permanent. The importance of careful selection of cases is stressed. Patients with organic mental deterioration or psychosis are excluded, as also are those with pseudobulbar palsy or those in whom the predominant symptoms are vegetative and akinetic rather than tremor and rigidity. Physiological senility and general medical contraindications are also considered to be important.

Mortality in 850 operations was 2·4%. Permanent hemiplegia developed in 3% of cases and transient hemiplegia in 6%. Some degree of somnolence and confusion occurred in 8% of cases during the first week and sometimes persisted for several weeks. A speech defect occurred in 7%, usually with recovery. Especially in cases of post-encephalitic Parkinsonism severe drowsiness, hyperpyrexia, hypokinesia dysphagia, pneumonia, and urinary retention may occur, but can be overcome by skilled nursing. Transient hyperkinetic states, usually of short duration, may occur, while a further complication is described as the "hyper-Parkinsonism crisis". The latter consists in an increase in all the preoperative manifestations of Parkinsonism apart from tremor and rigidity, and is thought to be due to mental and physical stress. It is therefore considered important to test the patient's reaction to stress and avoid operating on those whose tolerance is low.

A 5-year follow-up has been carried out on all the patients in the series. In no case has a circumscribed lesion in medial globus pallidus or ventrolateral thalamus produced a lasting emotional or intellectual defect or any motor or sensory defect, and the same is true of lesions in both situations on the same side. Although good results have followed the production of bilateral lesions, the quantitative limits within which they may be produced without the production of a defect have not been determined. *J. E. A. O'Connell*

NEUROMUSCULAR DISEASES

545. **Progesterone Metabolism in Myasthenia Gravis**
I. SCHRIRE. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **28**, 59–75, Jan., 1959. 2 figs., 21 refs.

There is not much doubt that the thymus gland is in some way involved in the causation of myasthenia gravis, and although the nature of this relationship is still somewhat obscure, thymectomy has been repeatedly carried out, with some measure of success, since 1941. That myasthenia gravis is also associated with the endocrine system is suggested by the fact that the severity of the disease diminishes in the last months of pregnancy, and that alterations in the symptoms may be observed during menstruation. The amelioration of symptoms during pregnancy appears to be related to the production of oestrogens and progesterone, which increases from about the third month to reach a maximum in the last month. The determination of progesterone levels in blood and urine is impracticable, but pregnanediol, an end-product of progesterone metabolism, can be estimated accurately, and the rate of progesterone production can therefore be gauged by determining the rate of urinary excretion of pregnanediol.

This method has been used at New End Hospital, London, in a study of the effects of thymectomy on progesterone metabolism in 49 cases of myasthenia gravis, pregnanediol excretion being determined in 10 both before and after thymectomy, in 16 only before thymectomy, and in 23 only after operation. The results indicate that urinary excretion of pregnanediol in myasthenia gravis is at the lowest limit of normal or below it; after thymectomy excretion increases rapidly, and within 3 weeks of operation it may be 4 times as great as before thymectomy. Two weeks later it may be 8 or 10 times the normal. The injection of corticotrophin in untreated myasthenia causes pregnanediol to be excreted in large quantities, but after thymectomy such an injection results in the excretion of normal quantities only.

Hugh Garland

546. **The Treatment of Myotonia: a Controlled Clinical Trial**
P. LEYBURN and J. N. WALTON. *Brain* [*Brain*] **82**, 81–91, March, 1959. 2 figs., 12 refs.

The object of the study here reported from the Royal Victoria Infirmary, Newcastle upon Tyne, was to compare the efficacy of quinine, procainamide, prednisone, and a placebo (lactose) in the relief of myotonia in 4 patients with myotonia congenita and 16 with dystrophia myotonica. Each drug and the placebo was given for 3 weeks (a total of 12 weeks), the periods following one another directly without a break, but the drugs were administered in varying sequence in different patients. In one 3-week period quinine was administered in a dosage of 5 grains (325 mg.) twice daily for the first week and then three times daily in the second and third weeks; procainamide in four daily doses each of 0·5 g. during the first week, 0·75 g. during the second week, and 1 g. during the third week, while the dosage of prednisone was 10 mg. twice a day throughout the 3 weeks. The degree of myotonia was determined by clinical examination and by electromyography, a uniform technique being used at all examinations.

In no case was the myotonia lessened during administration of the placebo. Quinine was the least effective of the three active drugs and caused side-effects such as tinnitus and deafness in several patients. Procainamide and prednisone were considered to be equally effective, 50% improvement or better being noted in 15 out of 20 patients while taking procainamide and in 15 out of 19 while taking prednisone. There were no side-effects with prednisone while procainamide caused only minor effects such as nausea, anorexia, and headache in 3 patients. In view of the possible dangers of long-continued treatment with prednisone the authors consider that procainamide is the drug of choice for the relief of myotonia.

J. W. Aldren Turner

Psychiatry

547. **The Inadequate Personality in Psychiatric Practice**
A. B. MUNRO. *Journal of Mental Science* [*J. ment. Sci.*] **105**, 44–50, Jan. [received April], 1959. 7 refs.

In this communication from Long Grove Hospital, Epsom, Surrey, the author points out that the term " inadequate personality " has no clearly defined clinical meaning and is often used to excuse a failure in diagnosis, prognosis, and treatment. In order to improve the clarity of the concept of inadequacy he has therefore applied a factor-analytic procedure in an attempt to discover relevant clusters of positively intercorrelated symptoms which would be distinguishable from clusters of psychiatric symptoms on the one hand and clusters of prognostically favourable traits on the other. The experimental group consisted of 200 patients who could be regarded as a representative sample of the mentally disordered population of Britain as a whole. Each patient was rated for the presence or absence of 246 traits which were operationally defined in terms of actual behaviour.

Statistical analysis of the resulting scores yielded 35 clusters of intercorrelated traits. Of these correlation clusters 5 were relevant to the investigation, since they showed low positive correlations with psychiatric syndromes and morbid personality types, and negative correlations with traits denoting a favourable eventual outcome. These five clusters of intercorrelated traits were interpreted as representing five types of inadequacy, these being as follows: (1) Patients of " low tenacity ", that is those who failed to carry out tasks which were well within their capacity, whose interests were changeable, and whose conduct was haphazard and manners " easy-going ". (2) " Egoic hypersensitivity ": inadequate patients of this type had a high opinion of themselves, could not admit mistakes, had a tendency to grumble, and often blamed others for the results of their own actions. (3) The third cluster was entitled " diminished social responsiveness "; such patients were stiff and stilted in manner and tended to withdraw from social contact. (4) The fourth type was characterized by " feeling avoidance "; these patients deprecated the display of emotions, did not form intimate relations with others, and suffered from a sense of deprivation. (5) The last cluster was termed " defensive denigration "; patients in this group had much in common with those in Type 2, but were more envious and resentful of people who enjoyed better success and fortune.

F. K. Taylor

548. **Involutional Melancholia. An Etiologic, Clinical and Social Study of Endogenous Depression in Later Life, with Special Reference to Genetic Factors.** [Monograph, in English]
Å. STENSTEDT. *Acta psychiatrica et neurologica Scandinavica* [*Acta psychiat. scand.*] **34**, Suppl. 127, 1–71, 1959. 39 refs.

SCHIZOPHRENIA

549. **Clinical Trial of Promazine Hydrochloride and Acetylpromazine in Chronic Schizophrenic Patients**
R. URQUHART and A. D. FORREST. *Journal of Mental Science* [*J. ment. Sci.*] **105**, 260–264, Jan. [received April], 1959. 17 refs.

The authors have investigated at the Royal Edinburgh Hospital two new phenothiazine derivatives, promazine hydrochloride and acetylpromazine, with the aim of ascertaining whether these drugs gave better results in chronic schizophrenia than other similar drugs or than weekly psychotherapeutic interviews. The trial was carried out on 39 male chronic schizophrenic patients aged 18 to 53 who had been in hospital for an average period of 13 years 4 months (range 3 to 24 years).

All 39 patients received lactose tablets during the first week, at the end of which 11 were then randomly selected to continue with the placebo and to attend psychotherapeutic interviews weekly for 6 weeks. The other 28 patients received acetylpromazine (75 mg.), promazine hydrochloride (100 mg.), and one lactose tablet, in each case three times a day for a period of 2 weeks, the order of administration of the drugs being decided by means of random numbers. During the 8th week all 39 patients received either amylobarbitone (50 mg. three times a day) or amphetamine (5 mg. three times a day). Finally each patient finished the course with 1 mg. of reserpine three times a day for 2 weeks or 100 mg. of chlorpromazine three times a day for 2 weeks, the order being again randomly determined. The scoring for behaviour, which took account of the patients' level of general activity, social activity, aggressive behaviour, and habits, was recorded each morning and evening by nurses to whom the nature of the trial had been explained.

In evaluating the results only changes which amounted to 25% of the control or placebo scores were considered as significant. On this basis acetylpromazine produced improvement in only one patient and promazine in none. Some of the other drugs were slightly more successful: thus reserpine benefited 8 (20%) of the patients, chlorpromazine 5 (13%), and amphetamine 4 (10%), but the most successful results were achieved with the weekly psychotherapeutic interviews, 5 (45%) of the 11 patients taking part in them being improved significantly.

The authors conclude that promazine hydrochloride and acetylpromazine are not going to replace reserpine and chlorpromazine and they suggest that as chronic schizophrenic patients are responsive to friendly interest and encouragement, good results might be achieved if their treatment included more psychotherapy, provided this is " directed within a conceptual framework regarding the nature of schizophrenia itself ".

F. K. Taylor

550. **The Relative Efficacy of "Vespral" and Chlorpromazine in the Treatment of a Group of Chronic Schizophrenic Patients**
G. P. WALSH, D. WALTON, and D. A. BLACK. *Journal of Mental Science* [*J. ment. Sci.*] **105**, 199–209, Jan. [received April], 1959. 17 refs.

A double-blind clinical trial was carried out at Rainhill Hospital, Liverpool, in order to assess the individual and relative effectiveness of "vespral" (triflupromazine, a new phenothiazine derivative) and chlorpromazine in the treatment of 66 female chronic schizophrenic patients, who were divided into three comparable groups of 22 patients, each member of a group being matched with a member in the two other groups in regard to age, years in hospital, "within-hospital adjustment", psychotic rating, and degree of withdrawal. The Within-Hospital Adjustment Inventory (devised by Egan, Walton, and Black) was designed to measure the social and occupational adjustment of hospital patients and the degree of nursing supervision required by them, the psychotic rating was made according to Rowell's graphic rating scale (*J. clin. Psychol.*, 1951, **7**, 3), while Venables's rating scale was used to measure activity-withdrawal (*J. ment. Sci.*, 1957, **103**, 430). The rating was carried out weekly by the sister in charge of each ward, who had no access to her own previous assessments. Since the scores for psychoticism and withdrawal were not numerically uniform and comparable a non-parametric test (the Wilcoxon Matched-Pairs Signed-Ranks Test) was used in the statistical evaluation of results. The three groups of patients were given orally tablets of either vespral, chlorpromazine, or a placebo in increasing doses during 8 weeks.

All three groups showed considerable improvement. Judged by the psychotic rating and withdrawal score there was no superiority of vespral or chlorpromazine over the placebo, nor did the effect of vespral differ significantly from that of chlorpromazine. However, according to the ward-sisters' clinical assessments the number of patients "much improved" by the tranquillizing drugs was twice that among those receiving the placebo. [This result is not statistically significant, but deserves consideration.] Investigation of the sedation threshold in 16 patients revealed no difference between that of vespral and that of chlorpromazine. Among the side-effects of vespral were drowsiness, pallor, Parkinsonian features, skin rash, facial oedema, and hypotension. The blood pressure fell in all three groups, but the hypotensive effect of vespral was the more marked and affected twice as many patients as did that of chlorpromazine.

The authors conclude that both drugs are of only limited value in the treatment of chronic schizophrenia.
F. K. Taylor

551. **Studies in Schizophrenia. I. The Various Developments in the Approach to Childhood Schizophrenia. II. Psychotherapy with Schizophrenics.** [Monograph. in English]
H. BRUCH. *Acta psychiatrica et neurologica Scandinavica* [*Acta psychiat. scand.*] **34**, Suppl. 130, 1–48, 1959. 41 refs.

TREATMENT

552. **The Use of Prochlorperazine (Stemetil) in Chronic Psychotic Disorders**
J. DENHAM. *Journal of Mental Science* [*J. ment. Sci.*] **104**, 1190–1194, Oct., 1958 [received Jan., 1959]. 1 ref.

In a trial reported from Whitchurch Hospital, Cardiff, prochlorperazine ("stemetil") was given in doses of 25 mg. 3 times a day to 59 patients with chronic psychoses —13 males who had been ill for an average of 13·4 years and 46 females who had been ill for an average of 8·3 years. Ten of the males and 30 of the females were violent, aggressive, and impulsive schizophrenics.

No improvement was observed in 18 cases. Those patients who responded favourably to the medication began to improve within the first 48 hours of treatment. Patients in whom delusions and hallucinations were prominent showed the most improvement, whereas maniacal patients and agitated depressives did not respond well. After a period of treatment varying between 30 and 150 days in responsive cases the dosage was halved. Most of these patients maintained their improvement on the half dose, and 21 continued to improve after prochlorperazine was withdrawn. In 19 cases the patient was able to return home, a maintenance dose being continued in 6 of these.

Among side-effects Parkinsonian symptoms were the most striking. They appeared after 3 to 90 days of treatment, but vanished soon after withdrawal of the drug and did not recur when its administration was resumed in the same dose together with 25 mg. of promethazine. Symptoms suggestive of peripheral vascular collapse developed in 4 cases; 3 further patients became drowsy, and one complained of increased excitement. *F. K. Taylor*

553. **A Clinical Trial Comparing Prochlorperazine ("Stemetil") with Chlorpromazine ("Largactil") in the Treatment of Chronic Psychotic Patients**
G. A. DRANSFIELD. *Journal of Mental Science* [*J. ment. Sci.*] **104**, 1183–1189, Oct., 1958 [received Jan., 1959]. 10 refs.

A trial was carried out at Warley Hospital, Brentwood, Essex, to compare the efficacy of prochlorperazine ("stemetil") with that of chlorpromazine ("largactil") in the treatment of aggressive male patients with chronic psychoses.

The average age of the 50 patients in the trial was 50·3 years (range 27 to 76 years) and their average stay in hospital 19·5 years (range 5 to 51 years). They were divided into two equal and comparable groups, paired so far as possible for aggression, disturbance, deterioration, age, ward, amount of electric convulsion therapy (E.C.T.) previously given, apathy, and aptitude for social activity and for occupation. Both groups were first given one inert tablet 3 times a day for 2 weeks, which produced hardly any clinical change in either group. Starting in the third week one group was then given one 12·5-mg. tablet of prochlorperazine and the other group one 25-mg. tablet of chlorpromazine 3 times daily, the dosage being increased in each group by

one tablet thrice daily each week except when it was clinically advisable to remain at the same dosage, to reduce it, or to withdraw the drug altogether. The maximum dosage in each group was 4 tablets 3 times a day, which was continued for 5 weeks. The three types of tablet were identical, and only the author and the chief pharmacist knew the nature of the medication. The assessment of clinical change in each case was based on the charge nurse's estimate in conjunction with the author's evaluation.

Improvement, mainly slight, was noted in 16 patients treated with prochlorperazine and in 19 treated with chlorpromazine, the difference between the groups not being statistically significant. The occurrence of side-effects of a Parkinsonian type was, however, significantly more frequent with prochlorperazine than with chlorpromazine, their incidence not being apparently related to the degree of clinical improvement or to the amount of E.C.T. previously received. There was one case of moderately severe jaundice with liver damage and two cases of syncope in the chlorpromazine group. Slight drowsiness was fairly common in both groups. Treatment with prochlorperazine had to be withdrawn in 6 cases because of side-effects during the trial, but only in 2 cases had chlorpromazine to be withdrawn. Treatment with prochlorperazine was continued after the end of the trial in 11 cases and with chlorpromazine in 17.

It is concluded that prochlorperazine has no clinical advantage over chlorpromazine in the treatment of this type of patient and that the greater incidence of side-effects seems to contraindicate its use.

F. K. Taylor

554. **A Controlled Investigation of the Effects of Cyclizine Hydrochloride in Chronic Psychosis**

B. G. FLEMING and J. D. C. CURRIE. *Journal of Mental Science* [*J. ment. Sci.*] **104**, 1219–1225, Oct., 1958 [received Jan., 1959]. 3 refs.

The authors report an investigation carried out at Powick Hospital, Worcester, to ascertain whether cyclizine hydrochloride, which is a popular remedy for motion sickness, also had a tranquillizing effect. For this purpose they selected 30 chronic deteriorated schizophrenic psychotics from amongst the 90 most disturbed male patients in the hospital. The patients were assigned at random to two treatment groups, one of which received cyclizine and the other a placebo during the first 2 weeks of the investigation, the treatment being reversed in the following 2 weeks. The tablets of cyclizine (50 mg.) and placebo (calcium lactate) were identical in appearance and only the dispenser knew which was which. Each patient received one tablet 3 times a day in the first and third weeks and double this dose in the second and fourth weeks.

The two groups of patients were found to be comparable in respect of such factors as diagnostic type, severity of illness, age, and duration of illness. Response to treatment was assessed on the basis of three different types of observation—a rating scale of psychiatric symptoms (which was found in preliminary tests to be fairly reliable), a clinical assessment, and a daily record of abnormal behaviour. The first two of these assessments were carried out by the authors, to each of whom 15 patients were assigned at random for rating purposes, while the behaviour records were kept by the nursing staff.

By none of the three methods of assessment could any statistically significant differences be demonstrated between the response to cyclizine and the response to the placebo. If anything, the placebo had a more beneficial effect than the drug, 41% of the patients being considered on clinical grounds to have improved while receiving the former and 28% while receiving the latter. It is therefore concluded that cyclizine has no specific tranquillizing properties.

[This investigation demonstrates once more that the unaccustomed degree of personal attention that the patient receives during a drug trial is of therapeutic benefit in itself.] *F. K. Taylor*

555. **Memory Disturbances after Electroconvulsive Therapy.** [In English]

B. CRONHOLM and C. BLOMQUIST. *Acta psychiatrica et neurologica Scandinavica* [*Acta psychiat. scand.*] **34**, 18–25, 1959. 7 refs.

In a previous paper (*Acta psychiat. scand.*, 1957, **32**, 280; *Abstr. Wld Med.*, 1958, **23**, 215) Cronholm and Molander reported the memory disturbances observed in patients 6 hours after electric convulsion therapy (E.C.T.) In this further communication from Karolinska Institutet, Stockholm, the authors describe the disturbances found in 30 such patients one week after E.C.T. The patients, who were aged from 20 to 64 years, all had relatively mild mental disturbances in the form of psychoneurosis or one or other type of depression, and had received a mean of 3·6 treatments over 10 days. As before, the paired-word test, the 20-figure test, and the short story test were performed a few days before and, in this study, one week after treatment. To these were added a letter–symbol pair test (which was designed to give further information on the hypothetical variable " retention ") and a vocabulary test to keep a check on the patients' intellectual levels. [For full details of these tests the original papers should be consulted.]

It was shown that one week after the course of E.C.T. there was a significant decline in the number of items reproduced 3 hours after learning (" delayed reproduction ") in both the paired-word and the figure tests. The letter–symbol pair test also revealed a decline in " retention " (calculated by dividing the number of items reproduced after 3 hours by the number recalled immediately), and an increase in " forgetting " (based on the difference between the number of items immediately recalled and the number remembered after 3 hours). No significant changes were noted in the results of the other tests as performed before and after treatment. A comparison of the present findings with those obtained in the previous study at 6 hours (*loc. cit.*) showed that the adverse effect of E.C.T. on memory " retention " is still present one week after treatment, although to a lesser degree. *E. H. Johnson*

Dermatology

556. **Dermatological Aspects of Sarcoidosis**
D. G. JAMES. *Quarterly Journal of Medicine* [*Quart. J. Med.*] **28**, 109–124, Jan., 1959. 7 figs., 30 refs.

After a short preliminary account of the historical background of sarcoidosis which well illustrates the protean clinical manifestations of this disorder the author reports from the Middlesex Hospital Medical School, London, a study of 200 patients who showed clinical or radiological features of sarcoidosis, supported by histological evidence of sarcoid tissue. The series included 33 patients (16·5%) with various skin lesions, 62 (31%) with erythema nodosum, and 105 who showed no skin involvement (the "non-skin group"). In addition attention is called to another 10 patients in whom histological evidence of cutaneous sarcoid tissue was unaccompanied by any evidence of the generalized disease; these lesions are termed local sarcoid-tissue reactions.

Sarcoid eruptions may be persistent or transient. Lupus pernio (of which there were 9 cases) and plaques (10 cases) persisted, whereas maculo-papular lesions (8 cases) and erythema nodosum were transient. In 6 instances skin scars from trivial accidents in childhood or following an operation proclaimed the disease by suddenly becoming purple and livid, and biopsy revealed active sarcoid tissue—a phenomenon suggesting a hypersensitivity reaction akin to erythema nodosum. Inoculation sites, especially that of an intradermal Mantoux test, may also contain sarcoid tissue. Cutaneous sarcoidosis is but one manifestation of a generalized disease, in which intrathoracic involvement is the most frequent accompaniment; the age of the skin lesions correlates with that of the intrathoracic abnormality. Erythema nodosum is accompanied by bilateral hilar lymphadenopathy, whereas lupus pernio and persistent plaques are associated with the later stages of diffuse pulmonary mottling. These trends are reflected in the incidence of radiological clearing, which is common with transient eruptions and rarely seen with long-standing skin lesions.

Other tissues commonly involved along with cutaneous sarcoidosis are the lymph nodes, eyes, bone, and spleen, in that order of frequency. Ocular and bone involvement is frequent in lupus pernio, and lymphadenopathy and splenomegaly occur with plaques and maculopapular eruptions. Bone cysts were observed only once in the absence of skin lesions, so that routine radiography of the hands and feet is of little diagnostic value. Granulomatous uveitis in the presence of skin lesions should always arouse the suspicion of sarcoidosis. It is pointed out that females preponderate among patients with skin lesions, though sarcoidosis affects the sexes equally.

In the 10 patients with sarcoid tissue in the skin only the Mantoux reaction was positive, the Kviem test negative, and the serum globulin level normal. Mantoux tests more often gave a negative result in patients with skin lesions than in those with erythema nodosum or those in the "non-skin" group, while the Kviem test gave a positive reaction in most patients with skin lesions, being particularly helpful in distinguishing the form of erythema nodosum due to sarcoidosis. In regard to treatment, the indications for corticosteroid therapy usually depend on the accompanying lesions and only to a lesser degree on the cutaneous process, but disfiguring lupus pernio warrants the use of steroids, though recurrence may follow cessation of treatment. Erythema nodosum is not an indication for steroid therapy, because recovery is complete without it.

[This is a valuable and comprehensive review.]

E. W. Prosser Thomas

557. **The Dermatology of Cardiovascular Disease.** [Review Article]
H. BEERMAN and T. PASTRAS. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **237**, 510–536, April, 1959. Bibliography.

558. **Malignant Melanoma. Personal Experience with 170 Cases**
E. M. DALAND. *New England Journal of Medicine* [*New Engl. J. Med.*] **260**, 453–460, March 5, 1959. 11 refs.

In this paper the author analyses his personal records of 170 cases of malignant melanoma seen during the past 30 years. In 40 cases the patient was seen in consultation only and was treated elsewhere. Of the remainder, 10 underwent secondary excision or other treatment for recurrent disease and 7 were untreated, while 113 were "treated for cure". The statistics of most interest are those for cases in which the preferred definitive treatment of wide local excision and very radical regional lymph-node dissection was carried out and the 5-year follow-up results were available. Neglecting the few who died from other causes, of 39 such patients in whom no tumour was found in the resected lymph nodes, 27 (71%) are without recurrence after at least 5 years, while of 27 in whom the nodes were involved, 7 (26%) are without recurrence. The combined survival rate was 52·3%.

[Although the series is too small for major conclusions to be drawn and is imperfect in some other ways, the total 5-year survival rate of 52% is impressive, while the salvage of one-quarter of the patients with involved lymph nodes provides strong support for those who believe in routine lymph-node dissection. Oddly enough, however, a similar 5-year survival rate of 55% (10 out of 18) was obtained in those cases (mostly of tumours of the head and trunk) in which only local excision was performed.] *Bernard Lennox*

559. **Does Serum Gonadotrophin Cure Acne Vulgaris?**
J. H. S. PETTIT. *British Medical Journal* [*Brit. med. J.*] **1**, 557–558, Feb. 28, 1959. 10 refs.

The literature on hormonal treatment of acne vulgaris is briefly reviewed and a controlled trial is then reported of serum gonadotrophin in 49 patients (29 male and 20 female) seen in the Department of Dermatology, Liverpool United Hospitals. The patients were divided into three groups according to the degree of acne—mild, medium, or severe. They were given tablets labelled A or B, and instructed not to swallow them but to allow them to dissolve in the mouth. The course of treatment lasted 12 weeks, and 40 of the 49 patients completed the course. In addition to the tablets, the patients received local treatment, including an application of 1% cetrimide or calamine lotion with 3% sulphur in mild cases and ultraviolet light in moderately severe cases. In cases of very severe acne tetracycline was also given by mouth.

When the results were analysed at the end of the trial it was found that of 21 patients given placebo (Tablet A) 9 were improved, 9 showed no change, and 3 were worse. Of 19 given serum gonadotrophin 8 were improved, 9 showed no change, and 2 were worse. Thus there was no evidence from this trial that administration of serum gonadotrophin by mouth had any effect on the course of acne already under treatment. *P. T. Main*

INFECTIONS

560. **Paronychia or Perionychia: Aetiological Aspects**
C. H. WHITTLE, J. L. MOFFATT, and R. A. DAVIS. *British Journal of Dermatology* [*Brit. J. Derm.*] **71**, 1–11, Jan., 1959. 7 figs., 15 refs.

The authors distinguish two forms of paronychia, primary and secondary. Primary paronychia is characterized by inflammation, often of sudden onset, of the nail-fold, with " bolster " swelling followed at a later stage by the formation of a pocket between the fold and the nail-plate, with or without damage to the latter. Healing is slow and relapse frequent, and more than one digit may be affected simultaneously or in succession. In secondary paronychia on the other hand the nail-folds " are merely participating in a low-grade chronic inflammatory condition of the skin of the fingers, as in degreasing dermatitis, atopic eczema, or psoriasis ". Whereas in the latter form " the infective element is minimal or non-existent ", evidence is accumulating that primary paronychia is predominantly due to infection with *Candida*, though *Staphylococcus aureus* and other organisms may be responsible for some cases.

A series of 104 cases of primary paronychia is here reported from the United Cambridge Hospitals, from 61 of which *C. albicans* or other species of *Candida* were isolated. *Staph. aureus* was isolated from 11 cases and other bacteria from another 11. It is observed that certain predisposing factors appear to be necessary to enable micro-organisms to thrive in the nail-fold. Foremost amongst these are maceration, trauma, and vascular changes such as those associated with perniosis, the menopause, and even constriction due to rings. Over 90% of the authors' patients were women and 57% were in the fifth and sixth decades of life. Treatment should be directed primarily towards protecting the hands from wet and rough work. It is emphasized that the active infection is in the nail-fold, any nail changes being essentially secondary; treatment of the nail-plate is therefore unnecessary in the authors' opinion. The prognosis is fair only; 50% of the authors' patients were free of their disability when last seen, the condition having persisted for an average of 1½ years in these cases and for 3 years in the remainder. One patient had a history going back 35 years. *Allene Scott*

561. **The Treatment of Dermatomycoses with Orally Administered Griseofulvin**
H. BLANK and F. J. ROTH. *A.M.A. Archives of Dermatology* [*A.M.A. Arch. Derm.*] **79**, 259–266, March, 1959. 6 figs., 13 refs.

Griseofulvin, a colourless, neutral, thermostable antibiotic, was first isolated from *Penicillium griseofulvin* in 1939 and since then its antifungal activity has been shown to be highly effective not only *in vitro* but also in plants and animals. In this preliminary report from the University of Miami School of Medicine, Florida, the authors report the results of the oral treatment of fungus infections in man with griseofulvin. Initially, the drug was given in a dosage of 4 to 5 g. daily, but subsequently this was reduced to 1 g. daily which was given in 4 divided doses.

The results of observation of 31 patients followed up for a sufficient period are summarized in a table and show uniformly good results in infections due to *Trichophyton rubrum*, *T. mentagrophytes*, *T. tonsurans*, *Microsporum audouini*, *M. canis*, and *Epidermophyton floccosum*. The treatment had no effect, however, on infections due to *M. furfur*, *Candida albicans*, and blastomycosis. The lesions of tinea corporis usually cleared in 1 to 2 weeks, and those of tinea pedis and of tinea capitis in 3 to 4 weeks. Onychomycosis, however, took 3 to 4 months to clear, and it was noted that infected nails and hair appeared to contain viable fungus in their distal portions until replaced completely by new growth. The drug proved to be of low toxicity in that no evidence of an antimitotic effect in the blood was seen, and apart from one case of urticaria only a few patients complained of minor abdominal discomfort and headache, which subsequently disappeared even while the griseofulvin was continued. The authors suggest, however, in view of the effects of large doses in experimental animals, that in cases in which griseofulvin treatment is likely to be prolonged, repeated blood counts should be performed as a precaution. They point out that the likelihood of relapse or recurrence of fungal infection is not yet known. *Benjamin Schwartz*

562. **The Pathogenesis of Superficial Fungous Infections in Cultured Human Skin**
H. BLANK, S. SAGAMI, C. BOYD, and F. J. ROTH. *A.M.A. Archives of Dermatology* [*A.M.A. Arch. Derm.*] **79**, 524–535, May, 1959. 11 figs., 28 refs.

Paediatrics

NEONATAL DISORDERS

563. **Perinatal Infections of the Central Nervous System.** [Review Article]
A. WOLF and D. COWEN. *Journal of Neuropathology and Experimental Neurology* [*J. Neuropath. exp. Neurol.*] **18**, 191–243, April, 1959. 12 figs., bibliography.

Spirochaetal, protozoan, viral and bacterial infections of the nervous system which occur in the perinatal period are described and discussed. These include congenital syphilis, toxoplasmosis, cytomegalic inclusion disease, herpes simplex infection, equine encephalomyelitis, and the bacterial meningitides and meningoencephalitides. Two cases of congenital toxoplasmosis, one of cytomegalic inclusion disease and 2 probable instances of herpes simplex infection are presented. In spite of the great number of infective agents which may enter and damage the central nervous system in the perinatal period, infection must still be considered to be one of the less common causes of pathological changes in the brain at this time of life.—[Authors' summary.]

564. **Changes in the Systolic Blood-pressure of Normal Babies during the First Twenty-four Hours of Life**
A. M. ASHWORTH and G. A. NELIGAN. *Lancet* [*Lancet*] **1**, 804–807, April 18, 1959. 3 figs., 11 refs.

In normal babies the systolic blood-pressure falls significantly during the first 24 hours of life. The range of the difference between the highest and lowest readings in 20 normal babies was 14 to 54 mm. Hg (mean 32). Delay in clamping the cord, to enable blood to be transferred from the placenta to the baby's circulation, delays the fall, but does not affect its magnitude. Clamping the cord has apparently no immediate effect; but in 7 of 12 cases studied there was a delayed rise in systolic pressure, reaching a peak 2½ to 13 minutes after the cord was clamped.—[Authors' summary.]

565. **Sphygmomanometer for the Newborn**
A. M. ASHWORTH, G. A. NELIGAN, and J. E. ROGERS. *Lancet* [*Lancet*] **1**, 801–804, April 18, 1959. 3 figs., 13 refs.

A sphygmomanometer has been designed to overcome the inherent difficulty and inaccuracy of the older methods of auscultation and palpation when used for measuring the blood-pressure in the newborn, and at the same time to avoid the complexity and bulk of the more sensitive pulse-indicators.

The method is visual. From a cuff inflated around the forearm the arterial pulsation is transmitted to an interrupted column of xylol in a glass capillary tube, giving rise to a characteristic movement of the xylol " beads ". Systolic pressures can be recorded with ease, and at intervals of a few seconds if desired, the range of error being at most 4 mm. Hg. Diastolic pressures cannot be recorded accurately with this instrument. The pulse-indicator fits into the box of a standard sphygmomanometer. The width of the occluding cuff used is 1 in. (2·5 cm.). This is an arbitrary choice, based largely on convenience, since no direct measurements of the arterial pressure have been made for comparison with the readings by the indireet method. The cuffs are made of polyvinyl-chloride sheeting, which is cheap, easy to make up, and easy to clean after use.—[Authors' summary.]

566. **Prolonged Neonatal Jaundice and Congenital Myxoedema.** (Ictère néonatal prolongé et myxœdème congénital)
M. BERNHEIM and J. BERTRAND. *Pédiatrie* [*Pédiatrie*] **14**, 161–169, 1959. 8 refs.

The authors present a retrospective study of 7 cases of congenital hypothyroidism in which there was prolonged neonatal jaundice. They occurred in a series of 73 cases of myxoedema seen at the endocrinological clinic of the Edouard-Herriot Hospital, Lyons, in recent years, thus representing an incidence of 9·6%; but the authors suggest that the true incidence is probably higher since some of these patients were seen only in later life and jaundice is often forgotten in histories compiled retrospectively.

In cases of this type the jaundice appears on the 2nd or 3rd day of life and always lasts more than one month, often several; in 3 of the present cases it lasted 2 months and in 2 for 3 months; in the other 2 cases the duration was not known. It varies in intensity and may appear only on weaning. The authors emphasize that breast-feeding delays the appearance of the signs of hypothyroidism. The serum indirect bilirubin level is raised, but that of direct bilirubin is normal. [Only one bilirubin estimation result is quoted, namely, one of 20 mg. per 100 ml.] The stools and urine are normal, and remain so. The authors attribute the jaundice to the same causes as that of physiological jaundice, that is, immaturity of the liver enzyme systems, particularly that of glycuronic acid transferase which is aggravated by the lack of thyroid hormone.

The differential diagnosis is discussed, and the difficulty of diagnosing hypothyroidism in the presence of jaundice is stressed. Though the condition is occasionally seen in premature babies affected infants are usually heavier than normal at birth. This fact, the persistence of jaundice in a large baby, and the fact that prolonged physiological jaundice most frequently affects premature infants and small babies, should raise suspicion of the diagnosis. Treatment with thyroid extract rapidly clears up the jaundice, which can, however, disappear spontaneously in the absence of such treatment. The prognosis in regard to intelligence is particularly poor; only 2 of the present 7 patients has an I.Q. over 90. The authors do not consider that this results from

damage to the brain from the high blood bilirubin concentration—for the clinical picture does not conform to that of kernicterus—but rather that jaundice as a manifestation of congenital hypothyroidism is evidence of severe and early deficiency of thyroid hormone.

H. G. Farquhar

567. **The Treatment of Hyperbilirubinemia of the Newborn with Sodium Glucuronate**

S. DANOFF, A. BOYER, and L. E. HOLT. *Pediatrics* [*Pediatrics*] **23**, 570–577, March, 1959. 6 figs., 29 refs.

It is now fairly well established that indirect-reacting bilirubin is toxic to the brain of the young infant, but that glucuronic acid renders the pigment more water-soluble, and thus facilitates its excretion from the body.

At New York University–Bellevue Medical Center, sodium glucuronate was administered to 25 newborn infants with serum bilirubin levels exceeding 9·5 mg. per 100 ml., of whom 16 had haemolytic disease. In all but 3 cases the salt was given intravenously in a 2 to 3% solution at rates varying between 100 and 250 mg. per kg. body weight per hour, the total dose ranging from 2 to 47 g. The serum bilirubin level was determined at least twice before treatment was started so as to estimate the rate of rise in concentration, and then frequently during and after treatment. In 17 patients the serum bilirubin level began to fall within 2 or 3 hours of the start of the infusion, the decline exceeding 5 mg. in 24 hours; in 4 the decline was slower or irregular, and in 4 the bilirubin level was not significantly reduced.

This study was undertaken in an effort to find a safer and more effective method of reducing hyperbilirubinaemia in the newborn infant other than by exchange blood transfusion. Previous studies in which glucuronic acid was given in relatively small doses by mouth had proved disappointing, but the authors consider that the present results with intravenous treatment and larger doses are more encouraging, and there were no complications. Comprehensive data for all the patients are presented in a table and a plea is made for further experimental trial of this method by critical observers. *F. P. Hudson*

CLINICAL PAEDIATRICS

568. **Primary Pulmonary Obliterative Vascular Disease in Infants and Young Children**

G. S. HUSSON and T. C. WYATT. *Pediatrics* [*Pediatrics*] **23**, 493–506, March, 1959. 10 figs., 44 refs.

The clinical features in 3 cases of primary pulmonary hypertension seen at Syracuse Memorial Hospital, New York, were studied in detail and correlated, in 2 of the cases, with the pathological findings. The patients were children, aged 3 to 4 years, and 2 were siblings for one of whom the pathological findings were, unfortunately, incomplete. The most prominent clinical symptom was marked dyspnoea on slight activity, which, the authors state, was noted in all proven cases in the literature. Fatigability and chest pain, which have also been reported, were present in 2 cases. The child may or may not be cyanotic. Right heart failure with systemic venous distension and enlarged pulsating liver are terminal events.

The pulmonary histopathological changes included obliterative intimal thickening in the smaller branches of the pulmonary arterial tree, principally in the arterial segment. In addition, the media of many small "muscular" arteries showed a striking increase in the amount of elastic tissue and occasional increased thickness of the muscular media. Lung sections from 8 infants who had died from fibro-elastosis showed no evidence of intimal thickening of the pulmonary tree. The authors suggest that the syndrome of primary pulmonary hypertension in infants and children is different in aetiology and course from pulmonary hypertension in older children, and that infection and acute arteritis play no part in the obliterative vascular changes. It is concluded that pulmonary neurogenic vasomotor disorders may be genetically determined. *J. M. Smellie*

569. **Specimens of Urine Obtained from Young Girls by Catheter versus Voiding. A Comparative Study of Bacterial Cultures, Gram Stains and Bacterial Counts in Paired Specimens**

C. V. PRYLES and N. L. STEG. *Pediatrics* [*Pediatrics*] **23**, 441–452, March, 1959. 3 figs., 16 refs.

The flora, bacterial count, and response to staining by Gram's method of paired catheter and non-catheter specimens of uncentrifuged urine were studied, the object being to determine "the diagnostic value of clean-voided samples and . . . the conditions under which cultures obtained from such specimens might be considered valid in the diagnosis of urinary-tract infections". The investigation was carried out in 3 groups of patients at the Boston City Hospital: Group 1, 58 females, aged 3 to 12 years, from whom paired catheter and clean-voided specimens of urins were obtained; Group 2, 62 female out-patients, aged 2 to 12 years, from whom clean-voided specimens were collected; and Group 3, 50 young girls admitted to hospital for various medical or surgical conditions from whom "random" non-clean voided samples of urine were obtained.

There was a 96·5% positive correlation between catheter and clean-voided specimens obtained by a standard technique from the same patients. From their findings the authors conclude that colony counts provide a valid means of differentiating infection from contamination in both clean-voided and catheter specimens from female children. They suggest that: (1) contamination is indicated if the urine contains less than 1,000 colonies per ml.; (2) infection is to be suspected if it contains between 1,000 and 100,000 colonies per ml.; and (3) infection is indicated if the urine contains more than 100,000 colonies per ml. "Clean-voided specimens are valid only if the patient is prepared before collection of the specimen as carefully as for catheterization". The results are considered to provide confirmation of previous findings that the "presence of organisms in Gram stains in the absence of epithelial cells from catheter or clean-voided specimens of urine is of diagnostic significance". *J. M. Smellie*

570. **Congenital Muscular Hypertrophy**
H. ZELLWEGER and W. E. BELL. *Neurology* [*Neurology (Minneap.)*] **9**, 160–166, March, 1959. 2 figs., 28 refs.

The literature on congenital muscular hypertrophy is reviewed and 3 cases are reported in this paper from the State University of Iowa Hospitals, Iowa City. Several different forms of congenital muscular hypertrophy must be distinguished: (1) hypertrophy associated with brain disease; it is suggested that constant innervation secondary to release of inhibition of the damaged cortex induces hypertonicity and hypertrophy of skeletal muscles; (2) Thomsen's disease or myotonia congenita; (3) muscular glycogen storage disease; and (4) benign idiopathic congenital muscular hypertrophy. The authors state that although previous workers have suggested that hypothyroidism may be one of the causes of congenital muscular hypertrophy, recent experience casts some doubt on this. Thyroid medication, may, however, have a beneficial effect in certain infants with muscular hypertonia and hypertrophy. *J. MacD. Holmes*

571. **Survivorship in Cerebral Palsy**
E. R. SCHLESINGER, N. C. ALLAWAY, and S. PELTIN. *American Journal of Public Health* [*Amer. J. publ. Hlth*] **49**, 343–349, March, 1959. 8 refs.

Surveys of the prevalence of cerebral palsy show that the rate diminishes with increasing age after adolescence. In Schenectady County, New York, it was found in 1948 that the prevalence rates for the age groups 5 to 9 and 10 to 14 years were 4·4 and 2·5 per 1,000 respectively, whereas in the age group 25 to 34 years the rate was only 0·8 per 1,000, while over that age it was 0·1 per 1,000. Accurate knowledge of survivorship in cerebral palsy is limited, but estimates based on clinical impressions have placed the mortality in the first 5 years of life as high as 15% compared with a rate of less than 5% in the general population.

During the 3 years 1950–2 compulsory notification of all cases of cerebral palsy was in effect in New York State (exclusive of New York City). Details were thus obtained of 3,299 individuals under the age of 18, from whom the 3,108 who were born before January 1, 1950, were selected for the present study of survivorship. During the 7½-year period of this study 119 deaths occurred among the 1,708 males and 86 among the 1,400 females. The over-all death rate for males was 9·6 per 1,000 person-years and for females 8·5 per 1,000 person-years. The male mortality was found to be 13 times and the female mortality 17 times greater than that to be expected in a general population of similar age distribution.

In 2,586 of the 3,108 cases the extent of the physical limitations was reported, and a study of mortality in this group provided further information. There was a marked increase both in the observed death rate and in the ratio of observed to expected deaths in each sex with increasing severity of physical disability. The mortality among those with severe physical involvement was 27 to 30 times greater than that expected in the corresponding age and sex groups of the population at large, while among those with mild physical involvement the mortality rate was 4 to 5 times greater than expected. No attempt was made to assess mortality according to the type of involvement since few patients had only one type, spasticity being combined in many cases with athetosis, ataxia, or rigidity. However, 15% of the cases were reported originally from State institutions for the mentally retarded, and the mortality in this group was 30 times greater than that of similar age groups in the general population. This excessive mortality was probably due to the high proportion of cases of severe physical involvement in this group as compared with the series as a whole. *J. Browne Kutschbach*

572. **The Natural Clinical History of Choreo-athetoid "Cerebral Palsy"**
P. E. POLANI. *Guy's Hospital Reports* [*Guy's Hosp. Rep.*] **108**, 32–45, 1959. 1 fig., 31 refs.

The author studied 73 patients with choreo-athetoid movements accompanying "cerebral palsy" (defined as "a persisting qualitative motor disorder appearing before the age of 3 years, due to a non-progressive interference with development of the brain") in order to obtain a clinical picture of the evolution of the neurological features.

In 38 cases the condition followed severe neonatal jaundice, due in 22 cases to Rh iso-immunization; in 35 no history of jaundice or of disturbance of pregnancy was elicited. The family histories were all non-contributary. There was a high incidence of prematurity in the cases not associated with Rh iso-immunization. In the group with no history of neonatal jaundice there was a high incidence of abnormalities of labour and of neonatal disturbance of feeding and oxygenation, neonatal fits, and vomiting. In most of the 73 cases neonatal symptoms had disappeared by the end of the second week of life, but feeding difficulties and respiratory stridor often persisted.

After the second month of life in most cases some neurological disturbance became evident. (1) In 8 cases this merely took the form of delay in development. (2) In 37 cases there were opisthotonic attacks, between which (with the exception of one case) the child was "floppy". The attacks became more frequent and severe until about the age of 9 to 11 months after which they often decreased in frequency and severity, being followed in about half the cases by a short phase of hypotonia and in the remainder by "unwanted" movements of the limbs. (3) In 25 cases the picture was of hypertonus, with relaxation only during sleep or at rare intervals during the day. This usually gave way to unwanted movements. (4) In 3 cases there was striking hypotonia with developmental retardation. By the end of the first year hypotonia was the main clinical feature in at least 23 cases, while others were hypertonic or exhibited only developmental retardation. Of the 58 cases in which the age of onset of unwanted movements could be estimated with reasonable accuracy, they appeared before the age of one year in 2, before 2½ years in 39, and between 3 and 3½ years in 17. The predictive value of the early findings in cerebral palsy is discussed. *R. Wyburn-Mason*

Medical Genetics

573. **A Test for Twins: the Identity of Their Reactions to Audio-visual Stimuli.** (Un test gémellaire: l'identité des réactions aux stimulations audio-visuelles)
L. GEDDA. *Annales d'oculistique* [*Ann. Oculist.* (*Paris*)] **191**, 752–766, Oct. [received Dec.], 1958.

In a series of experiments undertaken at the Gregorio Mendel Institute, Rome, the reactions of monovular and binovular twin pairs to various visual and auditory stimuli were studied. During the showing of a film to 31 monovular and 25 binovular pairs flashlight photographs were taken at intervals and the reactions of the members of each pair to various emotional situations compared. It was found that head attitudes were concordant in 87% of the monovular, but in only 61% of the binovular pairs. The position of the upper limbs was discordant to about the same extent in the two groups. Mimicry was concordant in a much higher proportion of the monovular (79%) than of the binovular pairs (32%).

To evaluate the degree of identity of twins' voices a recording was made of the voices of both members of each of 104 twin pairs (58 monovular and 46 binovular). Each twin in turn listened separately to the recording and was asked to say which voice was his own and which was his twin's. In 66% of cases among the monobular twin pairs neither member could make the distinction, whereas in only one case among the binovular twin pairs did both members fail to do so, thus demonstrating that the voices of monovular twins are concordant and practically identical in their acoustic effect.

A. A. Douglas

574. **The Genetics of Congenital Heart Disease and Situs Inversus in Sibs**
M. CAMPBELL. *British Heart Journal* [*Brit. Heart J.*] **21**, 65–80, Jan., 1959. 3 figs., 24 refs.

The author reports from Guy's Hospital and the Institute of Cardiology, London, that among about 2,000 families of patients with congenital heart disease 40 were found in which 2 or more cases occurred, the nature of the lesion being established conclusively in one of these cases and conclusively or fairly certainly in the other or others. The patients were sibs in 26 cases, parent and child in 9, and more distantly related in 6 (one family being included in the first two groups). In at least 7 families more than 2 cases occurred.

The families, which are briefly described, are divided into six groups. I. Those in which the patients were all cyanotic (5). They were sibs in 3 cases and first and second cousins in the other 2. Most of them had Fallot's tetralogy. II. Those with at least one case of situs inversus (which is regarded as recessively inherited) (5). Another cardiac malformation was also present in 4 of the 8 patients with situs inversus, and 6 of the patients were cyanotic. (Two of these families could have been included in Group I.) III. Those in which there was one case of Fallot's tetralogy and another of simple pulmonary stenosis (3), ventricular septal defect (one), or both (one). The patients were sibs in 4 cases and mother and child in the fifth. IV. Those with a case of Fallot's tetralogy and another of acyanotic congenital heart disease (one case each of aorto-pulmonary fistula, persistent ductus arteriosus, and atrial septal defect, and one in which the diagnosis was uncertain). In 2 cases the patients were sibs and in 2 parent and child. V. Those in which both affected members had acyanotic disease, but with different types of malformation (2). In one case the mother of a girl with coarctation of the aorta had a persistent ductus arteriosus and in the other the mother of a girl with a persistent ductus arteriosus had pulmonary stenosis. VI. Those in which the affected individuals had the same type of acyanotic heart disease (19). The common abnormality was "arachnodactyly and heart disease" in one case, coarctation of the aorta in one, aortic stenosis in 3, pulmonary stenosis in one, pulmonary stenosis and ventricular septal defect in one, persistent ductus arteriosus in 4, atrial septal defect in 2, and ventricular septal defect in 6. The patients were 2 sibs in 13 families (identical twins in 2 of them), 3 sibs in one, parent and child in 4, and child, mother, and grandmother in one.

The parents of one of 2 affected first cousins in one family in Group II and those of one pair of sibs in Group VI were first cousins—the latter family having short stature and broad hands and feet in 4 generations. There was no sex preponderance. The concordance of the cardiac abnormalities, which was certain in 14 and probable in 12 of the 40 families (and in 11 and 8 respectively of the acyanotic pairs), is regarded as highly unlikely to have occurred by chance, and more likely to be due to genetic than to environmental causes.

G. C. R. Morris

575. **The Mode of Inheritance in Essential Familial Hypercholesterolemia**
K. HIRSCHORN and C. F. WILKINSON. *American Journal of Medicine* [*Amer. J. Med.*] **26**, 60–67, Jan., 1959. 3 figs., 38 refs.

In this paper from New York University Postgraduate Medical School and Bellevue Hospital, New York, a study is reported of three pedigrees in which hypercholesterolaemia and xanthomatosis occurred in some of the subjects. Possible genetical interpretations are discussed, and it is concluded that the findings support the hypothesis that essential familial hypercholesterolaemia is transmitted by an incompletely dominant gene. In other words, it is held that heterozygotes for a particular gene have moderate hypercholesterolaemia, while homozygotes have marked hypercholesterolaemia associated with severe xanthomatosis and increased susceptibility to coronary heart disease and early death from myocardial infarction.

H. Harris

Public Health and Industrial Medicine

PUBLIC HEALTH

576. **Trends in Cancer Death Rates and Cure Rates**
E. C. HAMMOND. *Annals of Internal Medicine* [*Ann. intern. Med.*] **50**, 300–312, Feb., 1959. 9 figs., 4 refs.

Among females, the age-standardized cancer death rate has been on the decline in the United States and several other countries for the last decade or longer. On the other hand, the rate for males is still increasing. Most of this increase among males is due to the phenomenal rise in the death rate from lung cancer. The death rate from cancer of the uterus is declining quite rapidly in this country, presumably as a result of control activities. The death rate from stomach cancer is declining, apparently as a result of a decline in incidence rates. The reason for this is unknown. There is evidence that the 5-year survival rate for cancer has markedly improved during the past decade or two. The greatest improvement has apparently occurred for cancer of the colon, rectum, cervix uteri, corpus uteri, prostate and, to a lesser degree, cancer of the bladder.

It is estimated that about one-third of those who develop cancer in the United States today will be 5-year survivors, this being a considerable improvement over one-quarter being saved a decade or two ago. Unless some practical method of prevention is discovered and applied, the annual number of new cases of cancer per year in the United States will almost certainly rise steadily during the next 50 years as a result of the growth and aging of the population. This means that the need for medical care as well as facilities for cancer patients will inevitably increase. On the other hand, there is reason to believe that the cure rate can be improved (perhaps up to as high as 50%) by more effective use of present knowledge for the detection, diagnosis and treatment of cancer. This can be achieved only through the cooperative efforts of practically all branches of the medical profession. It is also apparent that effective application of preventive measures, as they are discovered by research, will depend upon the combined efforts of the medical profession as a whole.—[Author's summary.]

577. **Air Pollution and Causes of Death**
C. DALY. *British Journal of Preventive and Social Medicine* [*Brit. J. prev. soc. Med.*] **13**, 14–27, Jan., 1959. 4 figs., 10 refs.

A study is reported of the relationship between the death rates from respiratory and other diseases in middle-aged males in 83 county boroughs of England and Wales and indices of air pollution based on the amount of fuel burned in these boroughs. Fuel used for domestic purposes was distinguished from industrial fuel, and a method was devised to exclude the non-built-up areas of the county boroughs in calculating the average pollution per acre (0·4 hectare).

The indices of smoke and sulphur-dioxide pollution were so highly correlated that it was necessary to consider only one of these—namely, smoke pollution. There was a high correlation coefficient between domestic air pollution and bronchitis as a cause of death, 0·70, coefficients for other causes of death being pneumonia 0·60, respiratory tuberculosis 0·59, lung cancer 0·54, other respiratory diseases 0·27, and non-respiratory diseases 0·50. The coefficients with industrial pollution were considerably smaller. There was a positive correlation between the death rate from bronchitis and overcrowding and population density and an inverse correlation between this death rate and social class and education. When these social factors were eliminated by using partial correlations, it appeared that about one-third of the variation in mortality from bronchitis could be attributed to air pollution. The correlation between air pollution and deaths from lung cancer was lower than that between air pollution and deaths from bronchitis. An interesting finding was a positive correlation between mortality from lung cancer and that from respiratory tuberculosis.

An attempt was made to estimate the effect of sulphur gases by studying air pollution by power stations which are known to emit large amounts of these gases. The results did not indicate that proximity to a power station increased the death rate from bronchitis.

John Pemberton

578. **Antibodies to Asian Influenza and Influenza B: Edinburgh, 1958**
J. M. MCWILLIAM. *British Medical Journal* [*Brit. med. J.*] **1**, 473–476, Feb. 21, 1959. 4 figs., 11 refs.

Edinburgh experienced an epidemic of influenza due to Type B virus in December, 1954, and shared in the pandemic of Asian influenza in September, 1957. The author reports a serological study of the frequency of persisting antibodies against two strains of influenza virus, Type B (Lee) and Asian Type A/England/341/57, in a cross-section of the population within the city area. Specimens of sera were obtained from blood donors, patients attending antenatal and venereal disease clinics, hospital in-patients, nurses, and also from the community at large. Antibody titres were estimated by haemagglutination-inhibition tests and expressed as the reciprocal of the highest dilution of serum giving complete inhibition of haemagglutination.

Antibodies against Asian influenza virus were detected in 34·8% of 1,187 sera examined and against influenza B virus in 91% of 1,182 sera. The antibody titre to Asian influenza was highest in the age groups 11 to 15 years and almost at its lowest in the economically important age group 25 to 40 years. In contrast, the antibody titre to Type-B influenza virus was very low in children and rose to a high plateau in adults. In view of the low basal immunity in the age group 20 to 40 years, it is

suggested that a single booster dose of Asian influenza vaccine might be effective in protecting this group or the key members of the community within this age group.

D. Geraint James

INDUSTRIAL MEDICINE

579. **Occupational Dermatitis: Its Prevention, with Special Reference to Barrier Substances**

R. PORTER. *British Journal of Dermatology* [*Brit. J. Derm.*] **71**, 22–36, Jan., 1959. 1 fig., 8 refs.

An effective barrier cream must form a flexible film over the skin, capable of maintaining its integrity against outside contacts, and be at the same time free of damaging effects against the stratum corneum, sebum secretion, and hair follicles. Since none of the existing tests of the resiliency and resistant qualities of the film formed by barrier creams simulates practical conditions the author adapted for this purpose the Maeser water-penetration tester for leather, stout filter paper being impregnated with the test material and the rate of absorption of certain agents, such as carbon tetrachloride, measured. Special tests for protection against mineral oil and mild trauma were also devised. Unfortunately none of the substances commonly used as barrier creams gave very good evidence of efficiency under these conditions. The conclusion reached is that the main deterrent to industrial dermatitis must remain adequate cleanliness, thorough removal of contact irritants, replacement of natural skin greases, frequent supply of clean overalls and gloves, and adequate ventilation to obviate the effects of humidity and maceration. *Allene Scott*

580. **Report on Three Extensive Industrial Chemical Burns**

J. S. CASON. *British Medical Journal* [*Brit. med. J.*] **1**, 827–829, March 28, 1959. 2 figs., 13 refs.

Extensive chemical burns are rare; at the Burns Unit, Birmingham Accident Hospital, which serves a population of about four million, only 3 cases of extensive chemical burns have been seen during the last five years. Survival depends on the amount of skin destruction, the degree of absorption, and the toxicity of the chemicals to the kidneys and liver.

In this paper the author describes 3 cases of extensive chemical burns. The first patient, a man aged 47, had cresylic acid burns involving 15% of the body surface, mostly the lower part, but not of full skin thickness. He died on the eleventh day from renal failure. The second patient, also a man of 47, had chromic acid burns involving the whole of the right upper arm. These were almost full thickness except on the hand and axilla. The dead skin of the arm and forearm was excised 75 minutes after the accident and the areas were subsequently grafted. The patient was discharged from hospital 44 days after the accident. No kidney or liver damage and no other toxic effects developed. The third patient, a man of 62, had burns from hot acid nickel-plating solution affecting 40% of the body surface. He developed hypotension and oliguria of prerenal origin and died 5 days after the accident.

The problems presented by chemical burns are, first, those of thermal burns, with the added complication that the agent is often hot and caustic and, secondly, those of absorption and possible toxicity of the chemical. Measures to prevent absorption of the chemical or to remove it—namely, washing from the surface, neutralization, removal of the tissue reservoir (for example, excision of the skin and fat), detoxication or increasing excretion, are discussed in detail.

The author suggests that publication of short detailed histories of similar cases would be of particular help to those who have to decide whether surgical excision of a chemical burn is indicated. *R. E. Lane*

581. **Thalassaemia and Occupational Blood Diseases. I. Thalassaemia and Chronic Benzene Poisoning.** (Talassemia ed emopatie professionali. I. Talassemia e benzolismo cronico)

G. SAITA and L. MOREO. *Medicina del lavoro* [*Med. d. Lavoro*] **50**, 25–36, Jan., 1959. 4 figs., 14 refs.

The diagnosis of chronic benzene poisoning is not difficult when there is definite history of exposure and when the blood picture is that of normochromic or slightly hyperchromic anaemia, neutropenic leucopenia, and thrombocytopenia. The presence of primary blood diseases, however, may introduce variations into this blood picture which render the diagnosis uncertain. In some regions of Italy there is a high incidence of thalassaemia, which is compatible with good health but causes characteristic anomalies of the blood picture —morphological changes in the erythrocytes (aniso- and poikilocytosis, target cells, and punctate basophilia), hypochromia, hyperhaemolysis, hypersideraemia, increased osmotic resistance of the erythrocytes, and an increased proportion of alkali-resistant haemoglobin. There is usually a family history of the disorder.

In this paper from the Clinic of Industrial Medicine of the University of Milan 3 cases of chronic benzene poisoning are described in which thalassaemia was also present. In 2 cases the only features considered characteristic of benzene poisoning were moderate leucopenia and neutropenia, which persisted long after cessation of exposure, and transient remissions during transfusion therapy. The atypical features were the hypochromic character of the anaemia, the absence of thrombocytopenia, the presence of microcytic and target cells and of punctate basophilia, the hyperaemic bone marrow, the increase in the proportion of alkali-resistant haemoglobin, and the increased haemolytic index. In the third case exposure to benzene had been more intense and the changes in the blood picture were correspondingly more severe, the leucocyte count being 2,000 per c.mm., the erythrocyte count 1,300,000 per c.mm., haemoglobin level 21%, and the platelet count 100,000 per c.mm. The erythrocytes, however, showed the morphology characteristic of thalassaemia and there was a reticulocytosis of 9·5%, splenomegaly, and an erythroblastic bone marrow.

It is concluded that thalassaemia produces a profound modification of the blood picture of benzene poisoning and vice versa, and that carriers of thalassaemia are

highly susceptible to toxins affecting the haematopoietic tissues. It is therefore recommended that in order to eliminate this additional hazard pre-employment blood examinations should be carried out on persons living in regions where thalassaemia is endemic if they are likely to be exposed to substances such as benzene or radioactive materials. *Ethel Browning*

582. **Thalassaemia and Occupational Blood Diseases. II. Thalassaemia and Chronic Lead Poisoning.** (Talassemia ed emopatie professionali. II. Talassemia e saturnismo cronico)

G. SAITA and L. MOREO. *Medicina del lavoro* [*Med. d. Lavoro*] **50**, 37–44, Jan., 1959. 3 figs., 5 refs.

As with benzene poisoning [see Abstract 581] complexities of the blood picture arise when lead poisoning occurs in subjects of thalassaemia, as in the 3 cases here described in detail. All 3 patients presented with lead colic shortly after the beginning of their occupational exposure to lead; in one case the colic was so severe that it led to appendicectomy. In this case the erythrocyte count was normal but in the others it was slightly reduced, while in all 3 there was a low haemoglobin level, with microcytosis, poikilocytosis, target cells, punctate basophilia, increased osmotic resistance of the erythrocytes, and an increased percentage of alkali-resistant haemoglobin. Three sons of one patient carried the stigmata of thalassaemia, including a low colour index and punctate basophilia. The features common to lead poisoning and thalassaemia were those of increased bilirubinaemia, hypersideraemia, and punctate basophilia.

The diagnosis of lead poisoning was favoured by the simultaneous appearance of anaemia and episodes of colic, high protoporphyrinaemia, coproporphyrinuria, and greatly increased excretion of lead after the administration of calcium versenate (sodium calcium-edetate). The concomitant presence of thalassaemia was suggested by the persistence of punctate basophilia in spite of versenate therapy, the return of the hypochromia after removal from contact with lead, and the familial evidence of the disorder in one case. The relatively moderate diminution in the erythrocyte count was probably due to the fact that, in general, carriers of thalassaemia have some degree of erythrocytosis, and the relative mildness of the lead intoxication to the fact that thalassaemic subjects develop symptoms at an earlier stage than normal subjects. It is advised that persons showing the characteristics of thalassaemia should not be employed on processes involving exposure to lead.

Ethel Browning

583. **The Dust Content of the Lungs of Coal Workers from Cumberland**

J. S. FAULDS, E. J. KING, and G. NAGELSCHMIDT. *British Journal of Industrial Medicine* [*Brit. J. industr. Med.*] **16**, 43–50, Jan., 1959. 6 figs., 9 refs.

The authors observed that the lungs of coal-miners working in West Cumberland appeared much less black than those of miners in South Wales. Dust analysis was therefore carried out on the lungs of 33 Cumberland coal workers. No case of progressive massive fibrosis was found and it therefore seems that the condition is rare or absent in Cumberland. The composition of dust in the lungs from the two areas showed a broad similarity. The same minerals were present, but in the Cumberland miners the total amount of dust was less in the early stages of disease while the proportion of stone dust was greater and that of coal dust smaller. Also in these miners relatively more cases of silicosis were seen at necropsy. Thus rock dust appears to be comparatively more important in Cumberland than in South Wales in the production of pathological lung changes. Mine ventilation in Cumberland is better than in South Wales, but in the former area mechanical cutting which tends to increase dust concentration was introduced earlier. It may never be possible to determine with any accuracy whether between 1920 and 1950, when the bulk of disease with which this paper is concerned was produced, Cumberland coal mines were less dusty than Welsh anthracite or steam-coal mines. The possible effect of the type of coal being mined on the incidence of pneumoconiosis in different areas is discussed. *Kenneth M. A. Perry*

584. **Respiratory Function and Disease among Workers in Alkaline Dusts**

C. P. CHIVERS. *British Journal of Industrial Medicine* [*Brit. J. industr. Med.*] **16**, 51–60, Jan., 1959. 20 refs.

Since little is known of the possible effects of sodium carbonate dust on the lower respiratory passages 565 volunteers from 4 different works in the mid-Cheshire alkali industry were investigated during 1954 with regard to sickness absence and respiratory function, the latter by measuring the expiratory flow rate at 40 breaths per minute; of these men 339 were again similarly investigated in 1956. For the 2 years in question 188 and 89 men respectively had no dust exposure, but 134 and 83 respectively were exposed to soda ash. The average age for all groups was between 40 and 50 years; the proportion of subjects lapsing from the investigation was unfortunately high.

The number of weeks' absence as a result of respiratory illness averaged between 1·35 and 1·65 per man, except in those exposed to lime dust in 1956, among whom it was 2·21 weeks. The mean expiratory flow rate in the 188 men not exposed to dust in 1954 was 104·06 litres per minute, in the 134 exposed to lime dust it was 97·44 litres, and in the 243 exposed to soda ash it was 98·23 litres; the corresponding mean figures for 1956 were 106 litres (89 men), 100 litres (83 men), and 104 litres (167 men). Chest radiographs of 20 workers with long service and exposure to dust revealed no evidence of pneumoconiosis or other abnormality on miniature films.

These studies suggest that exposure to lime dust slightly increases the morbidity of respiratory disease, but that exposure to any alkali dust has no effect on the pulmonary function as measured by the expiratory flow rate. It was also found that older and shorter men had a greater impairment of expiratory flow rate due to heavy smoking (over 20 cigarettes per day) and that respiratory sickness absence was also increased in this group.

Kenneth M. A. Perry

Forensic Medicine and Toxicology

585. **An Investigation of the Distribution of Arsenic by the Sulphide–Silver Method**
G. E. VOIGT. *Journal of Forensic Medicine* [*J. forensic Med.*] **5**, 208–212, Oct.–Dec., 1958. 2 figs., 5 refs.

The sulphide–silver method for the histochemical demonstration of heavy metals, as described by Timm (*Dtsch. Z. ges. gerichtl. Med.*, 1958, **46**, 706), can also be used for demonstrating arsenic, and in this study reported from the University of Lund, Sweden, it was used to investigate the distribution of arsenic in the organs of (1) a 49-year-old woman who had died from arsenical poisoning, (2) a hamster which died of experimental acute arsenic poisoning, and (3) one hamster and one rat dying of chronic arsenic poisoning. A preliminary study showed that arsenic is precipitated by hydrogen sulphide in acid (but not in alkaline) solution, forming yellow arsenic sulphide, which can be demonstrated by the accumulation of metallic silver round the particles of arsenic sulphide. Thus black granules in the tissues fixed in acidified (formic acid) alcohol saturated with hydrogen sulphide were taken to represent the distribution of arsenic.

Tissue sections from the patient, hamsters, and the rat all showed a striking similarity. In the kidneys the arsenic was found mainly in the glomeruli and proximal convoluted tubules (and also in the walls of the capillaries between these tubules in the woman). In the liver, the black granules were seen mainly in the parenchymatous cells in the centre of the acini, and also sparsely in the Kupffer cells. In the pancreas arsenic appeared in the gland tubules and duct, suggesting that this organ is important in excreting the poison. The author points out that medico-legally the pancreas may prove a useful specimen for chemical investigation in cases of suspected arsenic poisoning. He concludes that " the sulphide–silver method cannot, of course, replace ordinary methods for the investigation of arsenic poisoning, but it does map out the sites of the substances precipitated by hydrogen sulphide ". *I. Berkinshaw-Smith*

586. **Detection of Methanol Poisoning, with Special Consideration of the Estimation of Formic Acid in Solid Viscera, Blood and Urine; Investigation of 11 Fatal Cases.** [In English]
A. R. ALHA, J. RAEKALLIO, and A. L. MUKULA. *Annales medicinae experimentalis et biologiae Fenniae* [*Ann. Med. exp. Fenn.*] **36**, 444–451, 1958 [received Feb., 1959]. 13 refs.

In an investigation at the Institute of Forensic Medicine, University of Helsinki, of 10 fatal cases of methanol poisoning and one case of combined ethanol and methanol poisoning the formic acid concentration in various internal organs (instead of in the urine only, as has been customary hitherto) was estimated by a modification of Fincke's method, which involves separation by steam distillation and gravimetric determination of the mercurous chloride reduced from mercuric chloride by formic acid.

In a preliminary experimental study on the viscera of subjects killed in accidents the recovery rate of added formic acid was of the order of 70 to 90% from the urine, brain, and kidneys, a little less (66 to 73%) from the liver, and 26 to 36% from the blood. Methanol was detected qualitatively in the steam distillate; the highest " normal " value for formic acidi n the organs was 5 mg. per 100 g. of tissue. This value was markedly increased in the cases of poisoning examined, reaching 300 mg. per 100 g. in the urine, 50 mg. in the brain, 76 mg. in the kidney, 54 mg. in the liver, and 30 mg. in the blood. *Norval Taylor*

587. **Potassium and Intoxication by Cardiac Glycosides.** (Калий и интоксикация сердечными гликозидами)
M. S. KUSAKOVSKIJ. *Клиническая Медицина* [*Klin. Med. (Mosk.)*] **37**, 35–39, March, 1959. 19 refs.

In circulatory failure retention of intracellular sodium and loss of intracellular potassium by the myocardium is primarily one of the biochemical effects of the failure itself. This effect may be potentiated by methods of treatment, for example, the administration of mercurial diuretics combined with a salt-free diet, ammonium chloride, acetazolamide, and ion exchange resins (even if they contain an assimilable form of potassium). An interdependence between the action of digitalis and the amount of intracellular potassium ions has been experimentally demonstrated. Digitalis can exert its optimum action only in the presence of an optimum concentration of potassium ions in the cells of the myocardium. Excessive doses of digitalis increase the loss of intracellular potassium ions and thus adversely affect myocardial function. In the presence of a low intracellular potassium concentration even small doses of digitalis can produce the picture of over-digitalization. This fact explains the appearance of the signs of over-digitalization which may follow a good response to diuretics, as well as the favourable effects of potassium chloride in such cases, and also the good response to potassium chloride therapy in cases of arrhythmia due to over-digitalization. In the study here reported the intravenous administration of potassium chloride (in the presence of either a high or low blood potassium level) to patients with arrhythmia resulted in a return to normal rhythm in 16 out of 21 patients previously treated with digitalis and in 22 out of 26 patients who had not received digitalis.

Hypokalaemia may also occur in case of adrenal cortical dysfunction, diseases of the kidneys and intestinal tract, and in insulin-treated diabetes mellitus; in such cases even small doses of cardiac glycosides may produce manifestations of over-digitalization.

In the author's method of treatment potassium chloride is given orally in a dose of 4 to 7·5 g. in syrup, water, or

fruit juice daily in divided doses and reduced or stopped when the therapeutic effect is attained. A serum potassium level of 3 mEq. per litre is aimed at, but is often difficult to achieve. The author recommends the intravenous administration of 40 mEq. of potassium chloride in 500 ml. of a 5% solution of glucose given over one hour, repeated if necessary up to a total of 120 mEq. and preceded by the slow infusion of 200 ml. of a 0·85% solution of sodium chloride, in cases of shock due to ventricular tachycardia, or ventricular rhythm preceding the development of ventricular flutter, in elderly over-digitalized patients unable to take potassium by mouth, and also in patients with paroxysmal tachycardia in the presence of atrio-ventricular block. Rare untoward reactions have included paraesthesiae, vomiting, and a paradoxical increase in the number of extrasystoles, and special care is necessary in the presence of renal disease. In spite of the usefulness of these preparations of potassium the Russian Pharmacopoeia includes only liquor kalii acetici and kalium bromatum, which are unsuitable for the administration of the relatively large amounts of potassium necessary in the cases described. *S. W. Waydenfeld*

588. **Aminophylline Poisoning in Children**
H. L. Bacal, K. Linegar, R. L. Denton, and R. Gourdeau. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] **80**, 6–9, Jan. 1, 1959. 7 refs.

The authors report the case histories of 10 children treated at Montreal Children's Hospital for toxic overdosage with aminophylline, which in most of these cases was being given for the treatment of asthma. Aminophylline consists of approximately 78% theophylline and 12% ethylenediamine, the combination resulting in increased solubility and better absorption of the theophylline. The latter is pharmacologically more active than the other well-known methylated xanthines, caffeine and theobromine, and acts on the central nervous and cardiovascular systems, while aminophylline relaxes bronchial smooth muscle and produces an increase in vital capacity in patients with asthma; its effects are cumulative. Overdosage with aminophylline gives rise at first to restlessness and irritability, but later tremors, convulsions, drowsiness, and coma may supervene. Other symptoms and signs are nausea, vomiting, haematemesis, increased urinary output, albuminuria, dehydration, cardiovascular collapse, and even death. The authors review some of the literature and comment on the unsatisfactory guidance given in medical textbooks regarding dosage of aminophylline for children. Maximum blood concentration of the drug occurs about one hour after oral ingestion of plain tablets and 5 hours after enteric-coated tablets. When given by rectal suppository its absorption is variable and unpredictable, but maximum blood levels are said to occur between 3 and 5 hours after administration.

Of the 10 cases described, which all occurred within a period of 5 years, the drug had been given by rectal suppository in 9 and in one case by intravenous injection. In the 6 cases in which it was known the total dose administered ranged from 225 mg. (3½ grains) per rectum for a 4½-year-old boy to 1,350 mg. (20¾ grains) in 36 hours for a 3½-year-old child. The patients almost all showed irritability, vomiting, haematemesis, and dehydration. As a result of their experience the authors recommend the following dosage in children: (1) by mouth as suspension tablets 5 mg. ($\frac{1}{13}$ grain) per kg. body weight, repeated if necessary every 8 hours; (2) by rectum as a suppository or retention enema 7 mg. ($\frac{1}{9}$ grain) per kg. body weight, repeated if necessary every 8 hours. In neither form of administration should the drug be given more frequently than every 6 hours, and the rectal route should be used only when oral treatment is not practicable. With this dosage schedule no undesirable effects have occurred and it has been adequate for the treatment of asthmatic children, excluding those in status asthmaticus.

The authors stress the dangers of combinations of drugs containing aminophylline, especially when ephedrine is a constituent of such a combination. They urge that the dosage of aminophylline should be clearly specified in milligrammes or grains per tablet or suppository and specified intervals for repetition of the drug should be stated. As there is no antidote to the drug the treatment of aminophylline intoxication is symptomatic, by sedation, the prompt correction of dehydration, and respiratory and circulatory support. It is considered that overdosage is much more common than hypersensitivity. *P. T. Main*

589. **Protection against Systemic Poisoning by Mustard Gas, Di(2-chloroethyl) Sulphide, by Sodium Thiosulphate and Thiocit in the Albino Rat**
S. Callaway and K. A. Pearce. *British Journal of Pharmacology and Chemotherapy* [*Brit. J. Pharmacol.*] **13**, 395–398, Dec., 1958. 4 refs.

The lethal effects of mustard gas, di(2-chloroethyl) sulphide, in the albino rat have been counteracted by "thiocit", a mixture of sodium thiosulphate and trisodium citrate in the ratio 10:1, administered intraperitoneally in a dose of 2·75 g. per kg. body weight. Thiocit afforded complete protection against greater than the median lethal dose of mustard gas whether given 10 minutes before or 10 minutes after mustard gas and raised the LD50 of mustard gas by approximately three times. The protection appeared whether the total dose of thiocit was given in one injection or serially over 30 minutes. The effective doses of sodium thiosulphate and of thiocit in rats were of the order of 3 g. per kg. body weight. Sodium thiosulphate alone and thiocit have been administered in single doses by slow infusion, by stomach tube and in drinking water. Both have shown activity by all routes of administration, but activity was greatest by intraperitoneal injection. The use of thiocit in conjunction with mustard gas therapy is suggested.—[From the authors' summary.]

590. **Chemical Testing Procedures for the Determination of Ethyl Alcohol**
T. E. Friedemann and K. M. Dubowski. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **170**, 47–71, May 2, 1959. 9 figs.

Anaesthetics

591. **Should Spinal Anesthesia Be Used in Surgery for Herniated Intervertebral Disk?**
J. W. DITZLER, P. R. DUMKE, J. J. HARRINGTON, and J. D. FOX. *Anesthesia and Analgesia; Current Researches* [*Anesth. Analg. curr. Res.*] **38**, 118–124, March–April, 1959. 8 refs.

In this paper the authors discuss their 20 years' experience and follow-up results of operations for prolapsed intervertebral disk at the Henry Ford Hospital, Detroit. Of the 1,062 patients reviewed, 736 received spinal anaesthesia and 326 general anaesthesia. The cases were re-examined not less than 2 months after operation and in most cases several years later. From the follow-up results it is concluded that spinal anaesthesia did not adversely affect recovery from operation. Of the 78 patients operated on under general anaesthesia with only fair or poor results at final evaluation 25 (31%) had persistent serious neurological signs, which might well have been falsely attributed to the spinal anaesthesia had this been employed. Of the 95 patients with similarly poor results who had received a spinal anaesthetic and who showed neurological sequelae the authors consider that these could definitely be attributed to the anaesthetic method in only one case and were possibly attributable to it in 6. The necessity for strict adherence to correct technique is stressed. *Mark Swerdlow*

592. **Use of Spinal Analgesia in Forceps and Breech Deliveries**
R. T. SEARS. *British Medical Journal* [*Brit. med. J.*] **1**, 755–758, March 21, 1959. 40 refs.

The author points out that in difficult obstetrical cases spinal analgesia has neither the limitations of local analgesia nor the disadvantages of general anaesthesia, and in this paper from the City Hospital, Nottingham, he describes the successful use of low spinal analgesia in 439 such cases (out of a total of 8,395 deliveries) between 1951 and 1955, 371 being forceps deliveries and 68 breech deliveries. (In a further 20 forceps cases and 29 breech presentations some other form of anaesthesia was used.) No maternal deaths occurred and, apart from headache, there were few complications, none of which were serious. Employing a carefully standardized, strictly aseptic technique, 0·8 ml. of 0·5% hyperbaric cinchocaine hydrochloride (" nupercaine ") is injected slowly between L3 and L4 to produce a " saddle-block " which results in complete sensory loss in the perineum, thighs, and lower abdomen, and diminished sensation in the uterine cavity. The relaxation of the perineum aids delivery and intra-uterine manipulations, and the conscious patient is able to assist delivery by use of the abdominal muscles, although there is a considerable loss of power and absence of the perineal reflex. Uterine tone is also retained, so that the risk of post-partum haemorrhage is reduced, the incidence of this complication being 7·5% (21 cases), in 11 of which the origin of the bleeding was thought to be cervical or vaginal tears. Manual removal of the placenta was necessary in 13 cases.

Inquiry showed that the method was satisfactory to the mothers, only one patient who had previously undergone lumbar puncture refusing this technique and another being unsuitable by reason of a lumbar kyphoscoliosis. In 13 cases analgesia was unsuccessful. There were 20 stillbirths and 7 neonatal deaths. Of 11 foetal deaths attributable to birth injury 8 occurred among the 371 forceps deliveries and 3 among the 68 breech deliveries, but none was related to the spinal analgesia; a further 3 deaths were unexplained. There was a notable absence of respiratory difficulty in the surviving babies. Asphyxia livida was present at birth in 20 babies and asphyxia pallida in 7, but in 18 out of these 27 cases factors such as foetal distress *in utero* and difficulty in delivery may have been responsible.

The maternal post-partum systolic blood pressure fell below 100 mm. Hg in 10 cases, in none of which, however, could it be attributed to spinal shock, which should be absent in a saddle-block of this nature. The blood pressure, recorded in 68 cases before and after delivery, did not show any consistent change. No case of meningitis occurred in this series, but headache was a frequent complication, being present in 62 (14·1%) of the patients. In 41 it was mild and did not last for more than 3 days, but in 5 it persisted for 2 to 3 weeks; the most useful of the measures tried for its relief appeared to be strict maintenance of the prone position. One patient had blurred vision and palsy of the external rectus muscle which persisted for 3 days, one developed a peroneal palsy following a difficult rotation and delivery by the Keilland forceps—these manœuvres being considered sufficient to account for it—39 patients suffered from temporary retention of urine, all but 3 responding to treatment within 48 hours, while 2 patients had partial urinary incontinence for one week. There were no cases of more serious neurological disorders, but these can occur and the author quotes the incidence and cause of those described in the literature. Finally, the advantages of spinal analgesia as compared with general anaesthesia and regional block in obstetrical cases are discussed. *Raymond Vale*

593. **Pudendal Nerve Block**
P. A. S. SAHAY. *British Medical Journal* [*Brit. med. J.*] **1**, 759–761, March 21, 1959. 9 refs.

The author describes the technique and results of pudenal block as performed in 102 vaginal deliveries at the General Hospital, Halifax. With the patient in the lithotomy position and 2 fingers in the vagina a 15-cm. pudenal needle is inserted midway between the anus and the ischial tuberosity and guided through the perineum,

the pudendal nerve being then blocked as it passes dorsal to the ischial spine by the injection of 5 ml. of a 1% procaine hydrochloride solution above the spine, of 3 ml. posterior to it, and of 2 ml. inferior to the spine; a further 5 ml. is injected around the ischial tuberosity to block the perineal branches of the posterior femoral cutaneous nerves, while the anterior labial branches of the ilio-inguinal nerve are blocked by the injection of 5 ml. of the solution above the clitoris. This whole procedure is then repeated on the other side. Pethidine hydrochloride in a dose of 50 mg. is now injected slowly into a vein and another 50 mg. given intramuscularly, allowing 3 to 5 minutes for the onset of anaesthesia. If labour pains are felt the patient self-administers trichlorethylene during uterine contractions.

Of the 102 deliveries performed under pudendal block as described, 48 were forceps deliveries requiring rotation, while in 27 the indications were maternal foetal distress, inertia, delay in the 2nd stage of labour, or maternal heart disease. Assisted breech deliveries numbered 15, of which one required forceps for delivery of the aftercoming head, but in the remaining 14, thought to be due to delay in the 2nd stage, natural delivery followed liberal episiotomy and maternal efforts without the use of forceps.

Induction of pudendal block by the vaginal route is next discussed, but the author compares it unfavourably with the method described above, since it fails to block the ilio-inguinal and posterior femoral cutaneous nerves, while the avoidance of infiltration of the skin makes repair after episiotomy easier. It has been said that pethidine in a dose as small as 100 mg. raises the pain threshold by 50%; the fall in arterial oxygen saturation of the infant's blood after the use of pethidine is not thought to be injurious. The intravenous injection of 10 mg. of nalorphine just before delivery to counteract respiratory depression has been recommended, but unfortunately this neutralizes the analgesic effect of pethidine. The author discusses the addition of adrenaline to the procaine solution in order to prolong its action but, in view of the fact that adrenaline abolishes uterine contractions and tone, and also because of its action on the maternal heart in combination with trichlorethyline, is not in favour of it. Lignocaine which was used on a few occasions in place of procaine proved very satisfactory.

[The injection of 50 mg. of pethidine intravenously and 50 mg. intramuscularly as described in this paper is said not to produce respiratory depression, though the present abstracter would be unhappy about this.]

Raymond Vale

594. **Epidural Anaesthesia in Obstetrics**

S. A. FLEMING and S. M. CAMPBELL. *Anesthesia and Analgesia; Current Researches* [*Anesth. Analg. curr. Res.*] **38**, 133–137, March–April, 1959.

At Toronto General Hospital epidural anaesthesia has been used for an increasing proportion of the obstetric procedures carried out there over the past 4 years. The technique employed is described in some detail. Spinal puncture is performed in one of the lower lumbar spaces, and after the epidural space has been located by the "hanging-drop" method the anaesthetic solution is then injected in 30 to 40 seconds and the patient turned on to her back. As agent the authors employ either 1·5 or 2% lignocaine or 1 or 2% hexylcaine, 15 to 20 ml. being used for vaginal deliveries and 25 ml. for caesarean section. An account is given of the complications which were encountered, the chief being those due to failure to inject the anaesthetic solution into the epidural space. The authors conclude that epidural anaesthesia is of considerable value in obstetrics. *Mark Swerdlow*

595. **New Technique with Hydroxydione. Experiences with "Presuren"**

A. H. GALLEY and L. H. LERMAN. *British Medical Journal* [*Brit. med. J.*] **1**, 332–337, Feb. 7, 1959. 4 figs., 25 refs.

In this communication from King's College Hospital and the Lewisham Group of Hospitals, London, the authors' experiences with "presuren", a recently introduced form of the steroid derivative hydroxydione, are described. Previously reported advantages of hydroxydione included a wide margin of safety, absence of respiratory depression, and quiescence of the laryngeal and bronchial reflexes; the disadvantages were its low solubility, the slowness of induction by intravenous drip because of the weak solution, a rise in pulse rate and fall in blood pressure in elderly patients, and a tendency to produce pain on injection and thrombophlebitis postoperatively. The last named disadvantage could be minimized by injecting a 2·5% solution into a fast running drip, or using a very weak solution (0·5%), but this kept the drug in contact with the vein wall for long periods. Recently stronger solutions (10%), preferably in 0·25% procaine, infused as rapidly as possible have been used successfully.

Presuren in powder form has a smaller particle size (50 μ) than hydroxydione and no soapy deposit to hinder its rapid dissolving in either water, physiological saline, or procaine solution. Tests showed that warm solutions appeared to have little additional value over cold solutions and were abandoned. Solutions in saline or water caused occasional pain passing up the vein, particularly if the vein was of fine calibre, but the use of 0·25% procaine solution as solvent prevented this in all but 2 of the authors' 165 patients. In those with very small veins the use of a 0·5% procaine solution is suggested. As proposed by Landau the authors employed a dosage of the order of 6 to 8 mg. per lb. (13·2 to 17·6 mg. per kg.) body weight in the normal patient, reduced to 5 mg. per lb. (11 mg. per kg.) for aged, cachectic, or underweight patients. Such doses produce an adequate level of basal narcosis without respiratory depression but require adjuvants such as nitrous oxide, cyclopropane, pethidine, or the usual muscle relaxants. With a weak solution and a long induction time laryngoscopy was possible by the time sleep occurred, but if the infusion was given rapidly to produce sleep in 3 minutes it was necessary to wait a further few minutes. Comparative respiratory tracings are reproduced to show the hyperpnoea followed by apnoea produced by thiopentone in contrast with the mild hyperpnoea followed by hypopnoea obtained with presuren. With rapid injection of 10%

solution the pulse rate showed little rise, in contrast with that seen after a bulky weak solution given by intravenous drip, this effect probably being due to the size of infusion. Little fall in blood pressure occurred unless doses in excess of 500 mg. were given, but in some patients postural hypotension could be induced when cyclopropane was used as adjuvant.

The incidence of postoperative thrombophlebitis was much reduced by the use of rapid injection and the authors found it was little higher than with thiopentone, for which they give the figure of 17 to 20%. Pain accompanying injection was associated with slowing of a drip, presumably owing to venous spasm; both effects were abolished by procaine. Discussing the value of this drug now that some of the obvious disadvantages of hydroxydione have been overcome the authors emphasize that after induction patients can be left safely in the care of ward attendants, as relaxation of the jaw and apnoea do not occur. They recommend its use for bronchoscopy and laryngoscopy, the initial cleaning or dressing of burns, and caesarean section. The drug is particularly valuable for anaesthesia in poor-risk patients. *Raymond Vale*

596. **Supplementation of Nitrous Oxide–Oxygen–Thiobarbiturate Anesthesia with " Pactal "**
E. M. KAVAN, V. L. BRECHNER, J. B. DILLON, and L. A. PARKER. *Anesthesia and Analgesia; Current Researches* [*Anesth. Analg. curr. Res.*] **38**, 75–84, March–April, 1959. 5 figs., 20 refs.

The authors have employed " pacatal " (pecazine) as a supplement to anaesthesia in the performance of 100 major operations (including laryngectomy, radical mastectomy, and ophthalmological and urological procedures) at the University of California Medical Center, Los Angeles. After premedication with morphine or pethidine plus atropine or scopolamine (hyoscine) anaesthesia was induced with thiopentone or thiamylal sodium. Nitrous oxide and oxygen (in a ratio of 3:1) were administered in a semiclosed circuit and, if required, an endotracheal tube was inserted. When the patient was settled a standard dose of 100 mg. of pecazine (except in very small or very large patients) was injected through the tubing of an intravenous drip. Additional doses of a thiobarbiturate (thiopentone or thiamylal) were given if the patient moved in response to surgical stimulation. Most of the operations did not require the use of muscle relaxants; the duration of surgery was commonly 2 to 3 hours.

The total amount of thiobarbiturate administered was considered to be greatly diminished in 60 patients and moderately reduced in 19; all these patients showed a normal rate of recovery from anaesthesia. In the other 21 patients the amount of thiobarbiturate required was not reduced and additional anaesthetic agents had to be employed to provide satisfactory anaesthesia; recovery in these patients was prolonged. In all the patients the blood pressure, pulse, and respiration were usually stable. Detailed histories of 2 cases and the results of electroencephalographic studies in 10 patients are presented. *Mark Swerdlow*

597. **Anaesthesia in Experimental Hypothermia below 20° C in the Dog.** (Anaesthesie bei Hypothermie unter 20° im Tierversuch)
E. KOLB, K. SPOHN, J. HEINZEL, and R. KRATZERT. *Anaesthesist* [*Anaesthesist*] **8**, 5–10, Jan., 1959. 6 figs., bibliography.

In experiments carried out at the Surgical Clinic of the University of Heidelberg 50 dogs were cooled in an ice-bath to a body temperature below 20° C. (range 19° to 13° C.) by the method of Ishikawa, Okamura, and Watarabe. [This group's only non-Japanese report has appeared in *Arch. klin. Chir.*, 1958, **289**, 232.] The circulation was then interrupted by clamping the great vessels and ventriculotomy or other intracardiac operation performed. After an average period of arrest of 49 minutes the circulation was re-established, the animal placed in a warm bath, and manual cardiac massage employed until the body temperature had risen above 20° C. and strong cardiac contractions had reappeared. In the entire series, ventricular fibrillation occurred only once before circulatory arrest. After the clamps had been released, however, ventricular fibrillation frequently occurred, but was invariably reversible by electrical counter-shock once the body temperature had risen above 20° C. Only 2 of the last 25 dogs operated on failed to survive.

The authors ascribe their good results to rigidly observed closed-circuit ether anaesthesia, maintained throughout at a deep level (Stage III, Plane 2). The depth of anaesthesia was at first assessed from clinical and electroencephalographic signs, but below 23° to 25° C. anaesthetic requirements were judged from the occurrence of arrhythmias. Whenever arrhythmias set in, the depth of anaesthesia was increased: this always suppressed the arrhythmias. *Gerald R. Graham*

598. **The Heat Mechanics of the Waters Canister**
J. C. AINLEY-WALKER. *British Journal of Anaesthesia* [*Brit. J. Anaesth.*] **31**, 2–14, Jan., 1959. 8 figs., 7 refs.

Writing from the Queen Elizabeth Hospital, Birmingham, the author presents an account of a well-conducted investigation into the generation and transfer of heat in the soda lime canister of a to-and-fro anaesthetic system. It was found that blackening the surface of the canister and adding a series of longitudinal copper fins to the outside considerably increased its ability to lose heat by radiation.

However, the desirability of thus increasing heat loss was next investigated, with the following results. Radiation from the surface of the canister accounted for about one-third of the total heat loss, and evaporation of water from its interior for rather more. Transfer of heat between the gases and the soda lime through which they passed was small, while the temperature of the inspired gases never approached that of the interior of the canister and always remained below body temperature. There is thus no possibility of heating of the patient by the inhalation of warmed gases, and though the dissipation of heat by radiation from Waters's canister can be increased by modification of its original design there is in fact no need to do this. *Ronald Woolmer*

Radiology

RADIODIAGNOSIS

599. **Vertebral Arteriography by Percutaneous Brachial Artery Catheterisation**
F. PYGOTT and C. F. HUTTON. *British Journal of Radiology* [*Brit. J. Radiol.*] **32**, 114–119, Feb., 1959. 12 figs., 3 refs.

Vertebral arteriography by direct percutaneous puncture sometimes fails and there is always some uncertainty as to the cause. The failure may be entirely due to technical difficulties, or the vessel may be too small to be entered by the needle, or it may be partly or completely thrombosed. But even successful puncture does not give information as to the condition of the artery proximal to the site of injection. The authors therefore describe their method of visualizing the vertebral artery by means of percutaneous brachial artery catheterization. The method is not normally recommended for investigation of the basilar artery system in cases of subarachnoid haemorrhage but may be used when direct puncture has failed. It is recommended in all cases in which thrombosis of the vertebral artery is suspected.

In carrying out the procedure local anaesthesia only is used and the appropriate brachial artery is punctured percutaneously at a point where it can easily be felt in front of the elbow. A Seldinger cannula (size P.R. 160) is inserted and the arm is abducted from the side to an angle of about 45 degrees, the elbow being extended. The brachial artery is then catheterized for a distance of 18 inches (45 cm.) from the site of puncture. Usually at about this distance the free passage of the catheter is felt to be checked, whereupon it is withdrawn slightly with its guide and the guide then completely withdrawn. The patency of the catheter is established by noting the backflow of blood, and saline solution is injected in the usual way to maintain patency. A pneumatic tourniquet is applied to the arm and held ready to inflate to a pressure greater than the systolic blood pressure immediately before the test injection of 10 ml. of 35% " hypaque ". Almost invariably it is found that the catheter had been checked at or near the origin of the vertebral artery, and satisfactory filling of this vessel is obtained at the first attempt. The left brachial artery generally gives less trouble than the right. When the test injection shows satisfactory filling films in the customary projections are taken to show the intracranial portion of the artery.

The use of concentrations of hypaque higher than 35% is not recommended. Separate injections each of 15 ml. should be used for each view; the total dose is not so high as it may appear, since some of the contrast medium is swept off into the brachial artery itself and the amount entering the vertebral artery is probably less than one-quarter of the total. Six illustrative cases are described and arteriograms reproduced. The authors consider that this method has great advantages over that described by Lindgren, in which the femoral artery is catheterized. It is also free from the danger of contrast medium being injected into the wall of the vertebral artery, which may happen in difficult cases and has occasionally caused death. *J. MacD. Holmes*

600. **The Postoperative Lumbar Myelogram**
M. L. SILVER, E. A. FIELD, C. M. SILVER, and S. D. SIMON. *Radiology* [*Radiology*] **72**, 344–347, March, 1959. 4 figs.

Myelography with 6 to 10 ml. of " pantopaque " (" myodil "; ethyl iodophenylundecanoate) was performed on 38 patients with continued or recurrent symptoms following laminectomy for herniation of a lumbar intervertebral disk and the myelographic and operative findings correlated. In 22 of the 38 cases the myelogram appeared normal, while in 16 it showed a defect which could be interpreted as a disk protrusion. In 11 of the latter the defect was at the same site as before the operation, the important differential diagnosis in such cases being between a recurrence, which requires operative treatment, and " arachnoiditis ", in which further operation is contraindicated. In the event all 11 patients were operated on and a definite recurrence of the herniation was found in all.

It is concluded therefore that a definite defect in a postoperative myelogram at the site of previous herniation indicates recurrent protrusion of the disk and not " arachnoiditis " or " adhesions ". *Arnold Appleby*

601. **" Chronic Appendicitis "—Some Radiological Observations**
G. OSBORNE. *British Journal of Radiology* [*Brit. J. Radiol.*] **32**, 174–179, March, 1959. 2 figs., 7 refs.

Although the concept of chronic appendicitis as a clinical entity is obsolescent, the diagnosis is still made and appendicectomy performed in an attempt to cure the symptoms attributed to it. A number of radiological signs have been stated to suggest chronic appendicitis, but there is little uniformity of opinion as to their value or significance in relation to the pathological findings or to the results of operation. The author has therefore compared the radiological findings in 50 patients who were later subjected to appendicectomy at the Middlesex Hospital, London, for chronic appendicitis with those in a control series of 50 patients who underwent appendicectomy incidentally in the course of a gynaecological operation and who had never had any symptoms which might have been attributable to chronic appendicitis. In each series the radiological findings were correlated with the findings at operation, and in the former series with the clinical results of operation. The control subjects attended for x-ray examination just before admission and were given two doses of 50% barium sulphate suspension in water—one the night

before and one on the morning of the examination, followed by breakfast and a saline purge. The patients with chronic appendicitis (the surgical series) received no overnight dose of barium sulphate, but the x-ray procedure was otherwise similar to that in the controls, a film being taken 8 hours after giving the barium, followed at 9 hours by screening and further films. If the appendix was visible a final film was taken at 80 hours; if not, the examination was repeated at 32 hours, the final film being taken at 80 hours only if filling was visible at 32 hours. Six months or more after operation a progress report was obtained on 42 of the 50 surgical cases, on the basis of which the series was divided into two subgroups: "cured" (24 cases), and "uncured" (18 cases). The findings were as follows.

	Surgical Series		Control Series (50 cases)
	Cured (24 cases)	Uncured (18 cases)	
Operation findings:			
Kinks	3	3	3
Adhesions to surrounding structures	11	8	4
Retrocaecal	12	10	20
X-ray findings:			
Caecum empty with 80-hour residue in appendix	8	7*	27
Concretions	4	5	22
Local tenderness	13	9	12

* In 3 cases the final film was taken at 56 hours and not at 80 hours.

Correlation between the x-ray and operation findings was poor. In a number of cases the lumen of a non-filling appendix was found at operation to be patent, whereas in others the appendix filled with barium despite partial obliteration of its lumen. A bulbous tip was observed radiologically in 3 cases and areas of narrowing in 7, in none of which could an anatomical explanation be found. On the other hand in 2 (control) cases the appendix was found at operation to have a bulbous tip filled with mucopus which had not been diagnosed radiologically because the distal end of the appendix had failed to fill. Local tenderness was less common in cases of recurrent acute appendicitis than in cases of persistent pain in the right iliac fossa, but this did not help in selecting cases which would benefit from surgery.

The author concludes that radiological examination gives no help in the diagnosis of either chronic or recurrent acute appendicitis or in determining whether operation will be of benefit. The difference in findings between the controls and the surgical series is explained by the fact that the abnormal x-ray findings probably partly determined the selection of cases for operation. There is strong presumptive evidence that the diagnosis was wrong in the 18 cases in which symptoms recurred soon after operation, while in the 24 "cured" cases it is possible that the short-term benefit obtained from operation was of psychological origin.

[This is an important paper, but apparently no amount of evidence will reduce the enormous number of unnecessary appendicectomies which are performed every year.] *Denys Jennings*

602. **"Chronic Appendicitis"—Some Pathological Observations**

A. C. THACKRAY. *British Journal of Radiology* [*Brit. J. Radiol.*] **32**, 180–182, March, 1959. 2 figs., 4 refs.

In this paper the pathological findings in the 50 cases of chronic appendicitis and 50 control cases investigated by Osborne [see Abstract 601] are reported. In each case the appendix removed at operation was fixed in 10% formol saline and then cut in slices $\frac{1}{8}$ in. (3·2 mm.) thick. A note was made of the size of the lumen, any abnormal contents, and the state of the walls. At least 3 blocks were then prepared from representative pieces of tissue and sections cut and stained with haematoxylin and eosin and by van Gieson's method. Only after the sections had been studied was the pathologist told anything about the clinical history.

Various pathological abnormalities were found, but with equal frequency in both groups. Nodules of faecal material sufficiently hard to merit the term faecolith were found in one appendix from each series. Threadworms were found in one of the control appendices. Two of the surgical series contained fruit pips—a raisin stone and a seed of raspberry type—while 2 of the control series contained hairs and a third contained an unidentified hard foreign body. A common finding was an ellipsoid bubble of gas, and it was considered that this might mislead the radiologist into diagnosing a faecal concretion. Mucopus was found in one appendix from each series. The histological appearances were as follows:

	Surgical Series	Control Series
Normal	15	13
Fibrotic	5	9
,, with inflammation	7	6
,, with partial obliteration	12	7
,, with complete obliteration	0	3
Acute inflammation	2	1
Chronic inflammation	16	17

Denys Jennings

603. **A Comparative Radiological Study of Reiter's Disease, Rheumatoid Arthritis and Ankylosing Spondylitis**

R. M. MASON, R. S. MURRAY, J. K. OATES, and A. C. YOUNG. *Journal of Bone and Joint Surgery. B.* [*J. Bone Jt Surg.*] **41**, 137–148, Feb., 1959. 25 figs., 17 refs.

Of the 53 patients with Reiter's syndrome previously reported (Murray *et al.*, *J. Fac. Radiol.* (*Lond.*), 1958, **9**, 37; *Abstr. Wld Med.*, 1958, **24**, 238) the authors, working at the London Hospital, have compared the radiological findings in 25 with the corresponding findings in 81 cases of rheumatoid arthritis and 38 of anky-

losing spondylitis. In all cases radiographs of the hands, feet, ankles (including the calcaneum), and pelvis were examined. Although the condition could not be differentiated radiologically in every case the following features were considered to be of value.

(1) In Reiter's disease exuberant periosteal new bone formation on the plantar surface of the calcaneum was considered to be characteristic. (A critical re-examination of 3 patients with rheumatoid and 2 with ankylosing spondylitis showing this feature indicated that in these cases the initial diagnosis was beyond suspicion in only one, and in this one case it was thought that Reiter's disease was present as well.) Of the patients with Reiter's disease this sign was noted in 20%. Similar but less marked changes may be observed round the wrist. Destructive joint lesions are common in the feet, but rare in the hands. Sacro-iliitis occurred in 32% and became more common with increasing duration of the disease, but unlike the other lesions it was usually symmetrical. Generalized osteoporosis was not a customary feature in this disease.

(2) In the radiographs of patients with rheumatoid arthritis the usual findings were confirmed. Peripheral arthropathy was slightly more common in the hands than in the feet and was accompanied by generalized osteoporosis. Sacro-iliitis did occur in 12% of these cases, but was later in onset and always less severe than in (3) ankylosing spondylitis, in which the predominant and early involvement of the sacro-iliac joints, observed in all cases, was found to be associated with peripheral arthropathy in the feet in 24% and in the hands in only 11% of these patients. In all three conditions posterior erosions of the calcaneum were sometimes seen and periosteal new bone formation was common round the malleoli.

Useful tables of distribution of the lesions in these conditions are given. Attention is also drawn to the age distribution; thus ankylosing spondylitis is earlier in onset, on the whole, than is rheumatoid arthritis, while Reiter's disease was found to occur in patients between the ages of 15 and 75, with its highest incidence in the fourth and fifth decades. *R. O. Murray*

604. **Radiological Manifestations in Tuberose Sclerosis**
P. H. WHITAKER. *British Journal of Radiology* [*Brit. J. Radiol.*] **32**, 152–156, March, 1959. 8 figs., 27 refs.

Tuberose sclerosis is characterized by epilepsy, mental retardation, and cutaneous manifestations, of which sebaceous adenomata are the most common. The disease is essentially the result of abnormal development of mesodermal tissues, and the changes may be very widespread. In this paper from the University of Liverpool, the author reviews the literature and reports 3 cases in which skeletal changes were observed; he points out that the association of skeletal defects may not be recognized unless specifically sought.

Radiology may be of value in demonstrating changes in the viscera, the brain, and the osseous structures. Visceral changes such as adenomata of the kidneys and intestines are seen as filling defects, while lesions in the liver and cardiac muscle present as alterations of outline. In the lungs there may be a coarsely marked and reticulated appearance with small cystic areas; this was indeed observed in one of the cases described. Such lesions may precipitate a pneumothorax. In the cerebrum, multiple areas of scattered calcification are the most common radiological sign; such calcification is discrete, but irregular in distribution. The osseous structures, which are of mesodermal origin, are commonly affected, but in varying degree. Reports in the literature indicate that skeletal lesions are diverse and inconstant in type; they have, however, also been described as fibrocystic, cystic, and sclerotic. Cystic changes are commonly seen in the terminal phalanges, and around these the presence of a sclerotic reaction is likely. Diffuse patches of sclerosis with poorly defined borders may occur anywhere throughout the skeleton, the skull being particularly affected. In one of the cases described by the author there was in addition considerable cortical thickening around some of the metacarpals. When such lesions are isolated, confusion may arise in the differential diagnosis from simple inflammatory lesions or osteoplastic metastases. The author suggests that the diagnosis may be established conclusively by demonstration of calcification in the skull, by the presence of skin lesions, and by a history of epilepsy.

R. O. Murray

605. **Radiological Bone Changes in Tuberose Sclerosis**
T. D. HAWKINS. *British Journal of Radiology* [*Brit. J. Radiol.*] **32**, 157–161, March, 1959. 8 figs., 15 refs.

The bone changes found in association with tuberose sclerosis are described with reference to 3 cases in adults seen at Manchester Royal Infirmary. The author also briefly mentions 2 cases of tuberose sclerosis (both patients being children) in which no bone changes were demonstrated.

In the skull hyperostosis of the inner table, particularly in the parietal region, may produce patchy areas of increased bone density. More generalized thickening and increase in density of both tables of the skull may also be observed. Secondary hydrocephalus with evidence of a raised intracranial pressure may rarely result from obstruction of the foramen of Monro by a subependymal nodule. In the hands and feet cortical thickening of the metatarsals and metacarpals may occur, producing an undulating contour. Cystic lesions, particularly in the terminal phalanges, are common and result from non-specific fibrous replacement of bone. In the cortex of the phalangeal shafts numerous small defects are often seen, which are sharply defined and vary in size; for this change the author suggests the term " cortical pitting ". The long bones may show irregular cortical thickening and coarsened trabecular pattern which may be indistinguishable from neurofibromatosis. Cystic changes and the development of small periosteal nodules have been observed by some workers. Circumscribed areas of bone sclerosis may also be seen. In the pelvis and spine patchy areas of increased bone density are well recognized manifestations of the disease.

The author states that these features of tuberose sclerosis rarely appear before puberty. He considers that the manifestations in the skull, hands, and feet are

characteristic and occur in combination in no other condition. The presence of these radiological bone changes may be of considerable value in establishing the true diagnosis in a patient presenting with epilepsy but in whom manifestations of tuberose sclerosis are only present as a forme fruste. *R. O. Murray*

606. **The Roentgenologic Manifestations of Meningiomas in the Region of the Tuberculum Sellae**
R. L. TUCKER, C. B. HOLMAN, C. S. MACCARTY, and M. B. DOCKERTY. *Radiology* [*Radiology*] **72**, 348–355, March, 1959. 10 figs., 8 refs.

In this paper from the Mayo Clinic the radiological findings in 51 patients who were operated on for meningioma of the tuberculum sellae are described. In 85% of the cases changes were detected on plain radiographs. In 26 (51%) these consisted in osteomatous changes in the planum sphenoidale, tuberculum sellae, anterior clinoid processes, or (in 4 cases) within the sphenoid sinus. Changes were found in the planum sphenoidale more often than in the tuberculum sellae, and in no case was the tuberculum involved alone. The authors suggest therefore that involvement of the tuberculum is secondary. Other changes seen in the plain radiographs included decalcification of the anterior or posterior clinoid processes or the floor of the sella turcica, decalcification of the posterior clinoid processes being the most common and often being combined with shortening of the dorsum sellae. Calcification within the tumour was seen in 4 cases, and in 2 it was so extensive as to outline the whole tumour. Posterior shift of the pineal body was observed in 2 cases, but in both these the tumour was large and of doubtful benignancy.

Carotid angiography was carried out in 17 cases, in the majority of which elevation and posterior displacement of both anterior cerebral arteries and the anterior communicating artery was noted. In one case the carotid siphon was shown to be erect and in 3 cases it was displaced backwards and downwards; 3 of these 4 patients had unusually large tumours. As a general rule the deep cerebral veins were not displaced, but the 3 large tumours displaced the internal cerebral vein backwards and upwards. In only one case was a diffuse concentration of the opaque medium demonstrated late in the arterial phase. Air encephalography was carried out only on 3 patients with exceptionally large tumours. *Arnold Appleby*

607. **Intracranial Meningiomas: a Roentgen Study of 126 Cases**
H. G. JACOBSON, H. W. LUBETSKY, J. H. SHAPIRO, and C. A. CARTON. *Radiology* [*Radiology*] **72**, 356–367, March, 1959. 21 figs., 19 refs.

A study is presented from the Montefiore Hospital and New York University College of Medicine of the radiological changes seen in 126 cases of intracranial meningioma at various sites. Changes were present in plain radiographs in 93 (77·5%) of 120 cases. Those suggesting a diagnosis of meningioma were: localized hyperostosis (41 cases), localized increase in vascularity (24), calcification (19), localized bone resorption (15), and localized spiculation (4), while those not specially suggestive of meningioma were decalcification of the dorsum sellae (27), and pineal shift (18). Multiple changes were noted in several instances. It is pointed out that the appearances in plain films are often so specific that the diagnosis can be made with reasonable certainty even before further investigations are carried out.

Air encephalography was performed on 46 patients, the commonest findings being shift of the septum pellucidum and localized deformity of a lateral ventricle. No features specific to meningioma were discovered. Carotid angiography was performed on 43 patients, with normal findings in only one case. Many varied angiographic appearances were demonstrated, some of the changes merely indicating a space-occupying lesion and some specifically suggestive of meningioma. The authors describe 8 types of change which they claim to be specific, a combination of 2 or more of these features being present in most instances. Sharply deflected arteries in the region of the tumour are said to be indicative of a tumour with well demarcated margins, and beaded, varicose-looking small arteries or fine, linear, wiry arteries within the mass to be suggestive of meningioma. The typical "cloud" or "blush" was encountered in 18 cases, and in 4 there were radiotranslucent defects within the "cloud". Filling of the external carotid artery was seen 22 times and a central arterial zone with peripheral venous drainage was seen on 16 occasions. There was an isolated example of a break in the superior sagittal sinus caused by pressure from the tumour.

It is claimed that the routine use of a rapid bi-plane film changer for angiography enables the number of injections of contrast medium to be reduced without loss of radiographic quality. *Arnold Appleby*

608. **The Significance of Bilateral Basal Ganglia Calcification**
J. C. BENNETT, R. H. MAFFLY, and H. L. STEINBACH. *Radiology* [*Radiology*] **72**, 368–378, March, 1959. 9 figs., bibliography.

In this paper from the University of California School of Medicine, San Francisco, the reports of cases of radiological demonstration of bilateral calcification of the basal ganglia which have appeared in the world literature up to the end of 1957 are analysed and 11 new cases added, bringing the total number up to 88. Calcification of the basal ganglia appears in the radiograph as a collection of opacities 3 to 5 cm. above the sella turcica in the lateral view and 2 to 4 cm. to either side of the midline in the antero-posterior view. The calcification is usually symmetrically bilateral, which helps in differentiation from pathological intracranial calcification in other sites.

In 58 (66%) of the 88 cases the serum calcium and phosphorus levels were abnormal, 42 of these 58 patients having idiopathic hypoparathyroidism, 14 pseudo-hypoparathyroidism, and 2 hypoparathyroidism following thyroidectomy. The remainder of the series was made up of 6 cases of familial idiopathic calcification of the basal ganglia, 5 of toxoplasmosis, 10 of miscellaneous

disease, and 9 in which no definite diagnosis was reached. Hypocalcaemia and hyperphosphataemia are findings common to idiopathic hypoparathyroidism, pseudohypoparathyroidism, and surgical hypoparathyroidism. In surgical and idiopathic hypoparathyroidism the deficiency of parathyroid hormone disturbs the regulation of phosphorus excretion, whereas in pseudohypoparathyroidism, although the hormone is secreted in normal amounts, renal response to it is diminished.

The clinical features of calcification of the basal ganglia include mental deterioration, grand mal seizures, cataracts, and tetany. All these were found with greater frequency in patients in whom calcium and phosphorus metabolism was abnormal—indeed the occurrence of tetany was confined to this group—and appeared to increase in severity with the duration of the metabolic disturbance. *Arnold Appleby*

RADIOTHERAPY

609. **Radiotherapy of Cancer of the Eyelid.** (Le traitement roentgenthérapique des cancers palpébraux)
F. BACLESSE and M. A. DOLFUS. *Journal de radiologie, d'électrologie et de médecine nucléaire* [*J. Radiol. Électrol.*] **39**, 832–840, Dec., 1958 [received March, 1959]. 13 figs.

This paper records the results in 414 cases of palpebral carcinoma seen at the Fondation Curie, Paris, between 1937 and 1950, of which biopsy showed the tumour type to be basal-celled in 303 cases and squamous-cell in 34. The 5-year cure rate was 73% (306 cases), and these cases are analysed according to site and size of the tumour. Of 96 patients with recurrence after surgery or radiation elsewhere 61 were well at 5 years, but 19 had a further recurrence; of these latter, 11 were treated surgically, in 9 cases without recurrence at 5 years. Out of the 414 patients 36 suffered recurrences *in situ*; 21 of these were subjected to operation, 18 being well after 5 years. Re-treatment by radiation is therefore possible, while cases not responding to radiation may be saved by surgery. Pre-auricular secondary nodes appeared in 7 of the 34 squamous lesions, and 5 of these patients died of metastases. Adenocarcinoma was rare (18 cases), but was radiosensitive; in 10 cases the tumour was a cylindroma associated with the lacrimal gland.

For lesions less than 1 cm. in diameter (280 cases) contact therapy was used (Philips or Chaoul), 4,000 to 4,500 r. being given over 3 or 4 weeks in single doses of 400 to 500 r. three times per week. Fractionation is important to obtain the best cosmetic results and to cause least damage to normal tissue. Larger lesions (134 cases) were treated at 150 to 180 kV., with fields delineated by a beam of light, and movable lead shields to protect as much of the eye as possible; these shields are preferred by the authors to contact shells under the eyelids. Careful set-up by the therapist is vital. For lesions measuring 1 to 3 cm., 4,000 to 5,000 r. was given over 4 to 8 weeks; for those over 3 cm., 4,000 to 6,000 r. over 6 to 9 weeks was given. Late keratitis was very rare. Cataract appeared in 4 cases, iridocyclitis and glaucoma in 5 (4 of them with extensive growths). X rays are considered the treatment of choice, and normally preferable to surgery or radium. *J. Walter*

610. **Carcinoma of the Base of the Tongue**
V. A. MARCIAL. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **81**, 420–429, March, 1959. 6 figs., 18 refs.

The author reviews 240 cases of carcinoma of the base of the tongue treated at the Oncologic Hospital, San Juan, Puerto Rico, and presents figures to show that in Puerto Rico cancer of the base of the tongue is more common than that of the anterior two-thirds. The incidence and age and sex distribution of the lesion are compared with those in other countries and aetiological factors are also discussed. Only in the last 2 years have such cases been treated by radioactive cobalt (^{60}Co) teletherapy, using lateral opposing fields and giving a tumour dose of 6,500 r. over 6 to 7 weeks. Treatment has previously mainly been by orthodox x-ray therapy at 200 to 250 kV., using lateral opposing and submental fields and delivering varying tumour doses ranging from 3,500 to 5,000 r. in 3 to 7 weeks. Since the introduction of ^{60}Co teletherapy the author has been impressed by the better response of the primary lesion.

In 80% of the present cases metastases were present at the time of admission. Owing to this high incidence of metastases, and to extensive disease in the majority of cases, only 11 patients survived for 5 years out of 135 followed for at least this period of time, but 36 of these patients had no treatment or only palliative therapy. Of these 11 five-year survivors one had been treated by surgery only, and another underwent operation after treatment with radium, the remaining 9 cases being treated by "orthovoltage roentgen therapy". Among 49 patients receiving palliative or incomplete treatment the average survival time was 7·5 months, with a maximum survival of 4 years. The author concludes with a plea for palliative treatment when radical treatment is not possible, as it appears to prolong survival.

M. P. Cole

611. **Five-year Results of Betatron X-ray Therapy**
T. A. WATSON and C. C. BURKELL. *British Journal of Radiology* [*Brit. J. Radiol.*] **32**, 143–151, March, 1959. 9 refs.

Between March, 1949, and May, 1953, the betatron with x rays of an energy of 22 or 23 MeV was used in the treatment of 114 patients at the Saskatoon Cancer Clinic, University of Saskatchewan. The betatron can produce x rays from fixed horizontal fields of any size from 0 to 15×15 cm. at 105 cm. F.S.D., the maximum dose in tissue being reached at 4·5 cm. depth. Output as used was 60 to 70 r. per minute. The treatment time, after a preliminary trial of a shorter period, was eventually fixed at 32 to 35 days. Selected groups of patients were treated, all of whom had advanced malignant disease for which conventional therapy was unsuitable.

In 18 cases of advanced cancer of the cervix a homogeneous dose of up to 8,000 r. in 5 weeks was delivered

to the whole pelvis, two pairs of opposed fields (antero-posterior, size 15×10 cm. or 15×15 cm., and lateral 10 or 15 cm.×10 cm.) being used. Of these patients, 7 remained well 5 to 7 years later. The only serious complication was diarrhoea. One patient, at the age of 65, fractured the neck of the femur a year after treatment, and another had two attacks of haematuria due to telangiectasia of the base of the bladder several years after treatment.

In a group of 45 patients with carcinoma of the bladder the authors have included all those treated up to the end of 1954. Many of them had very advanced disease and were in poor condition, while 34 had already received other forms of treatment. Attempts to deliver a tumour dose of 6,500 r. in 3 weeks produced severe complications, 5 out of 10 patients being unable to complete the course. The symptoms included severe diarrhoea with abdominal cramp, frequency of micturition, and general deterioration. The course was therefore extended to 5 weeks, with a tumour dose of 7,000 to 7,500 r. The fields were similar to those for the cervix, but the lateral fields were 8×10 cm. or 10×10 cm. in size. The results are discussed in detail. Of the 45 patients, 9 were alive 3 years after completion of treatment.

Of 26 patients with bronchogenic carcinoma given this treatment none survived 5 years; in 2, signs of a transverse myelitis developed 1½ to 2½ years after treatment. Other conditions treated included carcinoma of the body of the uterus (5 patients, 2 of whom survived 5 years), carcinoma of the vagina, cerebral tumour, and miscellaneous tumours.

The theoretical advantages of this form of irradiation are discussed. The authors were favourably impressed with the results in cases of carcinoma of the cervix and the body of the uterus, but the results in cases of bladder tumour were disappointing, although the area treated was approximately the same. They suggest that transplantation of the ureter before irradiation is started might give better results. *E. Stanley Lee*

612. **Radiation Therapy of Carcinoma of the Pancreas: Report on 91 Cases**

T. R. MILLER and L. M. FULLER. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **80**, 787–792, Nov., 1958. 27 refs.

The authors draw attention to the low cure rate and late diagnosis of cancer of the pancreas, both of which largely result from the anatomical position of the gland. Apart from total pancreatectomy as an attempt at radical cure, there are many palliative surgical operations. But the results have been disappointing, and many surgeons now consider that cholecysto-jejunostomy is as effective as pancreatic resection in relieving jaundice and pain and in increasing the period of survival. In the authors' series of 209 cases, seen at the Memorial Center, New York, nearly all of advanced disease, surgical exploration and biopsy were performed in all cases except those *in extremis* and side-track procedures carried out where advisable. After an average interval of 3 weeks radiation therapy was begun in 91 of these cases, the other 118 receiving no radiotherapy (although some had palliative surgery) and serving as a control group. The results in the 91 treated cases are analysed in relation to the various techniques employed and compared with those reported from other centres.

The best palliative results were obtained with 1,000-kV. x-irradiation, provided the treatment was given in the immediate postoperative period (within 2 or 3 weeks) and the disease was still fairly well localized to the pancreas and regional lymph nodes. In the control group of patients not receiving radiotherapy, the average survival time was 6·1 months and in the irradiated group it was 6·6 months after treatment was begun. However, as the authors point out, in the latter group many of the symptoms were relieved, particularly the pain, jaundice was reduced, and life in general was made more bearable, while in 9 cases (10%) "excellent" palliative results were obtained. The only contraindication to radiotherapy in these cases is persistent vomiting.

R. D. S. Rhys-Lewis

613. **Roentgen Treatment of Granulosa Cell Carcinoma of the Ovary**

R. B. ENGLE. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **80**, 793–798, Nov., 1958. 21 refs.

Writing from Los Angeles County Hospital, University of Southern California, the author points out that granulosa-cell tumours of the ovary are not rare. They constitute about 10% (reported range 1 to 19%) of all malignant ovarian tumours, 5 to 10% occurring before adolescence, about 30% during the child-bearing period, and 60% after the menopause. Histologically, the tumours are generally found to contain cells similar to granulosa cells, though some authorities consider that theca-cell elements are present as well. In these tumours, which vary considerably in size, the most common cellular patterns are the follicular, cylindroid, diffuse, and sarcomatoid—the last-named being sometimes indistinguishable from true sarcoma. Opinions differ as to the benignancy or malignancy of these tumours, and the prognosis is thus difficult to determine, late recurrences being common. The clinical course depends on the type of tumour, the signs and symptoms, and on the hormonal activity of the tumour, which is said to be maximal with the folliculoid and minimal with the sarcomatoid type. The primary treatment is surgical, and the author considers that both ovaries and the uterus should be removed where possible, this being followed by radiation therapy.

A series of 12 cases treated by surgery and radiotherapy are described in detail. Of these patients, who ranged in age from 3 to 70 years, 4 in whom there was rapid progression of the disease died within one year of surgery, one died after an operation performed elsewhere, and one after 2 years from recurrent tumour; but 2 were well after 3 years and 4 more alive and well after 12, 15, 16, and 18½ years respectively. These long survival times are considered to be due to the radiotherapy.

R. D. S. Rhys-Lewis